The American Journal of Cardiology

VOLUME III MARCH 1959 NUMBER 3

EDITORIAL

Drugs Which Alter the Metabolism of Vasoactive Monoamines

THIS discussion is concerned with cardiovascular drugs the pharmacologic actions of which are related to changes in tissue levels of monoamines such as serotonin (5-hydroxytryptamine) and norepinephrine. In this regard, localization of these amines in the animal body is of interest. Both compounds are found in the central nervous system with the highest concentrations being in the primitive portions of the brain, particularly the hypothalamus. Peripherally, serotonin is found chiefly in the gastrointestinal mucosa which is its major body depot; small amounts also occur in the blood platelets. Peripheral norepinephrine is found in association with adrenergic nerve fibers. The relative content of norepinephrine in different organs has an obvious correlation with the adrenergic nerve supply. Aside from the adrenal glands and spleen, the highest concentrations of norepinephrine are in the heart and blood vessels, both arteries and veins.

These amines have been referred to as central neurohumoral agents. The role of peripheral serotonin is not established. Norepinephrine is considered to be the adrenergic neurotransmitter substance. The pharmacologic effects of elevated circulating levels of these amines on the cardiovascular system are revealed in patients with malignant carcinoid and pheochromocytoma. Although serotonin is a potent stimulant of smooth muscle in the intestine, bronchi, and blood vessels, its actions on human blood pressure are variable and complex. The general effects of norepinephrine on the circulation are largely determined by its vasoconstrictor action and the reflex slowing or direct stimulant action on the heart. It is doubtful that one can simulate by infusion technics, however, the physiologic effects which occur when formation and metabolism of these amines are changed at endogenous sites in various organs.

To the present, serotonin itself has not been found to be a useful drug. On the other hand, following the recognition of norepinephrine as a natural vasoconstrictor, clinical experience showed it to be an effective and relatively nontoxic vasopressor agent in the treatment of hypotensive states, including cardiogenic shock.

METABOLISM OF THE AMINES

The concentration of these amines in tissues represents a balance between formation, storage, and destruction. Alterations in the first factor will not be discussed, since it has not been shown as yet to be affected at a chemical level by cardiovascular drugs. The mechanisms of tissue storage are poorly understood but are markedly altered by drugs such as reserpine. Oxidative deamination catalyzed by the enzyme(s), monoamine oxidase, is important in the physiologic disposition of both agents. Under normal conditions, conversion of serotonin to 5-hydroxyindoleacetic acid (5HIAA) by monoamine oxidase is the predominant means of inactivation. In the case of norepi-

nephrine, recent studies have shown that methylation of the 3-hydroxy position is also involved, with the major metabolic products being 3-methoxynorepinephrine, 3,4-dihydroxymandelic acid, and 3-methoxy-4-hydroxymandelic acid.

Release of the Amines by Reserpine

Reserpine, as well as other active rauwolfia alkaloid preparations, is widely used in the therapy of hypertension and neuropsychiatric disorders. The administration of large doses of reserpine to animals produces a marked increase in the urinary excretion of 5HIAA due to a depletion of body stores of serotonin, the serotonin of the brain and platelets being especially sensitive to release. It is thought that the action of reserpine is on tissue-binding sites, since no alteration in the biosynthesis or metabolism of the amine has been demonstrated. The pharmacologic effects of reserpine in animals, such as sedation, miosis, hypothermia, and hypotension, have an inverse relationship to the level of brain serotonin and persist for several days, whereas the drug itself disappears from the brain within a few hours. Because of the relative resistance of intestinal serotonin to reserpine release, it has not been possible to detect significant release of serotonin from the gastrointestinal tract of humans with reserpine. However, we have found that as little as 1 or 2 mg of reserpine per day lowers the level of platelet serotonin to negligible amounts within 7 to 10 days in patients with normal or elevated levels of platelet serotonin.

Norepinephrine in the brain is also reduced by reserpine in the same fashion as is serotonin. Reserpine also causes a release of norepinephrine from peripheral sites such as the adrenal gland and heart, the latter organ being very sensitive in this respect.

It seems reasonable to assume that the actions of reserpine are in some way related to its ability to release amines from central and peripheral tissues. It would appear that release of norepinephrine from the adrenergic nervous system is involved in the production of hypotension by the drug.

Monoamine Oxidase (MAO) Inhibitors

The enzyme, MAO, is found in most tissues. Inhibitors of this enzyme have been shown to block the conversion of serotonin to 5HIAA and to alter the metabolism of norepinephrine. When inhibitors are administered to animals, the brain levels of both serotonin and norepinephrine are found to rise. Similarly, increased levels of norepinephrine have been demonstrated in the heart.

The inhibitor which has been most widely studied is isopropyl isonicotinyl hydrazine (iproniazid). This compound was relegated to temporary clinical obscurity when therapeutic trials in patients with tuberculosis revealed it to be more toxic than its analogue, isoniazid. However, it has recently been introduced again, this time in the therapy of neuropsychiatric states. A major "side effect" of the drug is postural hypotension, and hence it is also being used with some success in the treatment of hypertension. Of great interest is the recent discovery by Cesarman that administration of the drug to patients with angina pectoris results in dramatic relief of pain. A favorable action of the drug in angina pectoris has been confirmed by several workers but its eventual usefulness is not yet apparent. Also, there have been reports of hepatic toxicity due to the drug.

Regardless of the eventual role of iproniazid in cardiovascular therapy, it is important to determine whether its effects on blood pressure and angina pectoris are specifically related to inhibition of MAO. Accordingly, we have set up an extensive screening program in experimental animals and man in order to discover other MAO inhibitors and to evaluate their actions on the cardiovascular system.* A large number of inhibitors have already been found in studies on animals, the most potent of these being the harmala alkaloids. The development of a simple chemical method of screening these drugs at the clinical level became desirable.

Study of Monoamine Inhibition in Man

Although we have found increases in platelet serotonin levels and decreases in urinary 5HIAA values during iproniazid therapy in man,

* In collaboration with Drs. L. Gillespie, T. P. Waalkes, S. Udenfriend, H. Weissbach, and B. Witkop.

the changes were small and variable. The findings in this laboratory of: (1) large amounts of serotonin and norepinephrine in bananas and (2) an alternate and efficient pathway of metabolic disposal (by O-glucuronidation) of serotonin in animals given iproniazid has served as the basis for the development of a simple procedure for detecting MAO inhibition in man. The test consists of the administration of large amounts of serotonin orally and measurement of urinary 5HIAA during control and experimental (drug trial) periods. Using this test it has been possible to demonstrate in man MAO inhibition with iproniazid and a variety of other inhibitors. The physiologic and therapeutic corollaries of MAO inhibition are currently under investigation.

Conclusions

The actions of some cardiovascular drugs appear to be related to changes in the metabolism of monoamines in organs such as the heart and brain. It is likely that further investigations of the type discussed here will lead to the development of other useful drugs.

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Experimental Studies

Angina Pectoris

III. Demonstration of a Chemical Origin of ST Deviation in Classic Angina Pectoris, Its Variant Form, Early Myocardial Infarction, and Some Noncardiac Conditions*†

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CLASSIC angina pectoris and its variant form[1,2] differ in clinical and other aspects. One striking evidence of this difference is the ST depression in classic angina and the ST elevation in the variant form. The presence of this difference in the two syndromes suggests that chemical differences in the myocardium are worth investigating. A number of experiments therefore were devised to evaluate chemical changes in the myocardium. Two hundred twenty-four dogs were used in the following 10 experiments.

EXPERIMENTS

1. "WASHING" EFFECT ON ELEVATED ST SEGMENT

Epicardial ST elevation was produced in 63 dogs by coronary artery ligation or by direct epicardial injury. Areas showing ST elevation then were "washed" with normal saline solution at body temperature (Fig. 1). As soon as washing with the normal saline solution was started, the ST elevation began to diminish in amplitude in 62 of the 63 dogs. In some experiments ST elevation disappeared completely within a few beats, the ST segment becoming isoelectric (Fig. 2A). This reduction in ST elevation amplitude persisted as long as the washing was continued. As soon as the washing was stopped, the ST segment usually rose rapidly to its previously elevated position (Fig. 2B). A statistical analysis of the diminution in height of the ST segment during washing showed the results to be highly significant statistically ($P < 0.005$).

The probable explanation for the phenomena described above is that ST elevation is caused by some chemical or electrochemical process of unknown nature and that unknown processes responsible for the ST elevation can be altered by saline solution. The factor of inducing the change in the electric field should also be considered.

2. "WASHING" EFFECT ON DEPRESSED ST SEGMENT

Similar experiments were carried out in 11 dogs with epicardial areas of ST depression of 2–3 mm in depth produced by hypotension to as low as 40 mm Hg mean pressure.[2] Washing these areas with normal saline at body tempera-

* Preliminary report.

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This work was aided by grants from the U. S. Public Health Service and the L. D. Beaumont Trust Fund.

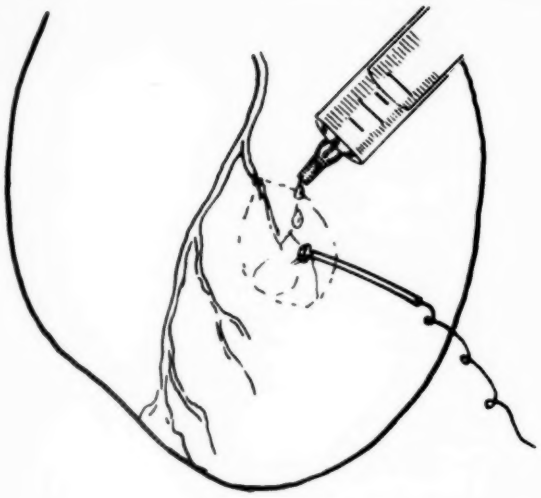


Fig. 1. Technic of "washing" with normal saline at body temperature.

logic differences in the two conditions. Early electrocardiograms after myocardial infarction are identical usually with those of the variant form of angina. It is suggested that similar changes occur in both conditions.

3. CHEMICAL ANALYSIS OF PERFUSATE OF ISCHEMIC† MYOCARDIUM

In order to find out whether a substance is "washed" away, chemical analysis of the perfusate was performed. In 20 mongrel dogs a branch of the anterior descending coronary artery was ligated, producing an area of epicardial ST elevation. In 5 other dogs hemorrhagic hypotension of sufficient degree was induced to give epicardial "islands" of ST depression.[2] Normal saline solution at body temperature was poured over areas of ischemic epicardium, the ischemic

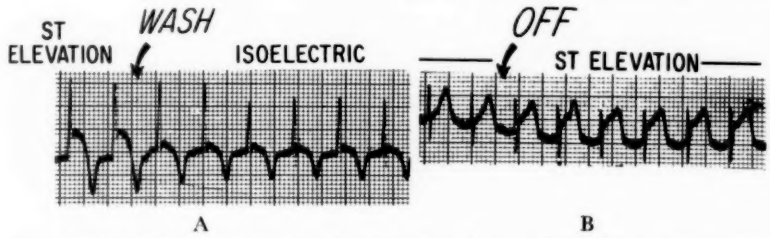


Fig. 2. (A) ST response to "washing" with saline. ST elevation decreases or disappears when the injured area is "washed" with normal saline. (B) When "washing" is discontinued, ST elevation returns promptly.

ture failed to produce any observable alteration of the ST segment depressions in 10 of the 11 experiments (Fig. 3) (statistical value, $t = 0.115$).

Washing the epicardium of control animals in which no ST deviations were present produced no significant change in the level of the ST segments.

It would appear, therefore, that there is a chemical basis for the production of ST segment deviations. It would also appear that ST elevations are fundamentally different from ST depressions in their chemical processes, since washing with normal saline reduces ST elevation but does not affect ST depression.*

This finding also indicates a chemical difference (of unknown nature) between classic angina pectoris with its characteristic ST depressions and the variant form of angina with its typical ST elevations. These chemical differences would appear to be due to marked physio-

areas being judged on the basis of either ST elevation (due to ligation of the coronary artery) or ST depression (due to hypotension).

The perfusate was collected, analyzed chemically for 12 substances, and compared to control perfusates in the same animal before bleeding. Chemical and spectral analysis of the perfusates did not reveal any statistically significant change in previously present substances, such as potassium, or any new substances which might be responsible for ST segment elevation or depression occurring with either of these two technics.

4. ST SEGMENT RESPONSE TO PADS SOAKED IN VARIOUS SALINE CONCENTRATIONS

In 5 dogs a branch of the anterior descending coronary artery was ligated, producing an epicardial ischemic area with ST elevation. A

* Washing with hypertonic saline eliminated ST segment depression and brought it to the isoelectric line.

† The term "ischemia" in this report is used in its physiologic sense expressing insufficient blood supply to the myocardium.

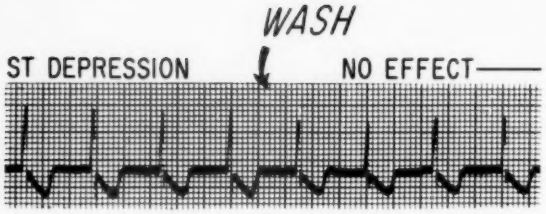


Fig. 3. "Washing" has no effect on ST depression.

gauze-covered electrode soaked in isotonic saline solution was applied to the area of ST elevation. Hypertonic (1.0%) saline solution (171 meq Na/L) then was poured over the same gauze. This action resulted in diminution of ST elevation, without significant change in the level of peaks of R waves (Fig. 4A).

The same experiment was performed using hypotonic (0.6%) saline solution (103 meq Na/L). This resulted in a further *increase* in the already *elevated* ST segments, without significant change in QRS amplitude (Fig. 4B).

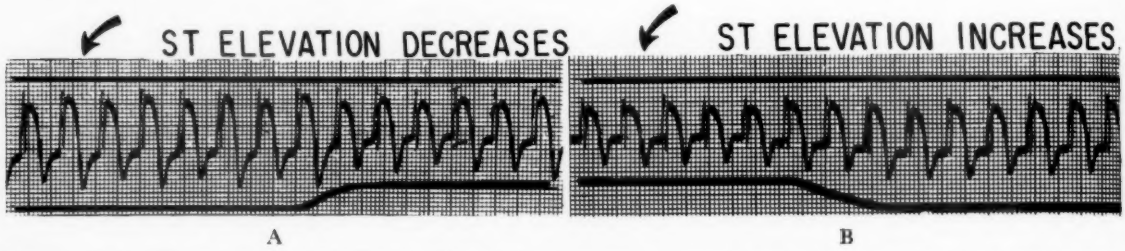


Fig. 4. (A) ST response to hypertonic saline. Gauze-covered electrode soaked in isotonic saline solution was applied on the area of ST elevation. Then when hypertonic saline solution (1%) was poured on this gauze-covered electrode, there was a decrease of ST elevation, without significant change in the level of peaks of the R wave. As mentioned in the text, displacement of the T-P level is responsible for the ST segment deviation. (B) ST response to hypotonic saline. Gauze-covered electrode soaked in isotonic saline solution was applied on the area of ST elevation. When hypotonic saline solution (0.6%) was poured on this gauze-covered electrode, ST elevation further increased without significant change in the level of peaks of R waves. This increase in ST segment elevation was relative to the downward displacement of the T-P segment. Lines at bottom of each tracing are exaggerated for purposes of illustration.

In other experiments, cotton-tipped electrodes were soaked in saline solutions of various concentrations in place of the gauze-covered electrodes, and similar results were obtained.

In general these changes in the ST segment were relative to the level of the T-P segment. Close analysis revealed that it was the T-P segment which actually deviated upward on perfusing with hypertonic saline and downward with hypotonic saline. This problem is being investigated further.

In all preceding and succeeding experiments described in this paper, T-P deviation was found predominantly responsible for the ST segment displacement. This will be referred to as *ST deviation*, it being understood that T-P deviation was responsible. A partial explanation of ST segment response in experiments 1 and 4 was that ST segment deviation is altered by change in electrical field induced by an electrolyte solution applied to the epicardial surface. However, other factors affecting ST deviations, especially changes in chemistry, cannot be excluded.

5. INTRA- AND EXTRACELLULAR NA AND K CONCENTRATIONS IN ISCHEMIC ST DEPRESSION

The first four experiments suggest that changes in sodium and potassium concentrations may be involved in ST deviation. Therefore, chemical analysis of the myocardium was performed. Sections of myocardium were obtained from 11 dogs as noted:

(1) Control sections of myocardium from areas with isoelectric ST segments in normotensive animals before bleeding. The animals were then bled until "islands" of ST depression appeared.

(2) Sections of "islands" of ST depression after bleeding.

(3) Additional control sections of myocardium from interinsular areas with isoelectric ST segments in the same animals made hypotensive by bleeding.

Sections 1, 2, and 3 were obtained from each animal and were subjected to chemical analysis.[3]

TABLE I

Intra- and Extracellular Water Potassium and Sodium Concentration (meq/L)

Exp. No.	Control *ST isoelectric*				After bleeding							
					ST depressed				*ST isoelectric*			
	Na^+		K^+		Na^+		K^+		Na^+		K^+	
	Intra[a]	Extra[b]	Intra	Extra	Intra	Extra	Intra	Extra	Intra	Extra	Intra	Extra
34	9.4	150	125.6	4.1	0	153	136	4.8	0.9	153	134	4.8
	MEMBRANE POTENTIAL[c]				MEMBRANE POTENTIAL				MEMBRANE POTENTIAL			
	74.7 mv		79.5 mv		∞ mv		74.0 mv		138.0 mv		75.1 mv	
52	20.1	157	118	4.5	4.3	151	155	5.5	20.8	151	138	5.5
	55.5 mv		88.3 mv		96.5 mv		90.3 mv		54.2 mv		87.3 mv	
53	1.8	156	151	4.0	5.5	152	158	3.8	16.3	152	143	3.8
	121 mv		98.3 mv		89.5 mv		100.5 mv		60.5 mv		94.5 mv	
75	22.1	151	162	3.5	19.2	149	146	4.6	28.0	149	122	4.6
	52.5 mv		95.0 mv		55.3 mv		92.5 mv		45.3 mv		88.5 mv	
86	6.9	161	150	4.3	6.5	159	147	4.4	9.9	159	144	4.4
	85.0 mv		95.6 mv		86.5 mv		94.3 mv		75.0 mv		94.3 mv	
93	29.1	148	122	4.6	22.1	147	128	3.9	17.6	147	123	3.9
	44.3 mv		88.4 mv		51.6 mv		94.3 mv		57.7 mv		93.5 mv	
104	19.7	152	154	4.0	11.0	144	156	4.0	7.6	194	182	4.0
	55.5 mv		95.7 mv		73.5 mv		98.5 mv		80.0 mv		103.0 mv	
109	11.8	155	132	4.6	11.8	152	141	3.9	16.4	155	136	4.6
	73.5 mv		90.7 mv		68.7 mv		98.5 mv		61.5 mv		91.5 mv	
117	7.4	136	158	3.7	0	133	140	5.1	19.3	133	151	5.1
	78.5 mv		101.0 mv		∞ mv		90 mv		52 mv		91.4 mv	
123	13.8	156	132	4.2	14.2	143	148	4.8	15.0	143	149	4.8
	70.7 mv		93.2 mv		62.5 mv		93.0 mv		61.5 mv		93.2 mv	
129	10.7	155	144	4.6	11.0	152	148	4.2	11.6	152	128	4.2
	71.7 mv		92.6 mv		70.7 mv		96.0 mv		69.5 mv		92.0 mv	

[a] Intracellular. [b] Extracellular. [c] Potential calculated at 37°C.

There was a decrease in intracellular Na^+ concentration and increase in intracellular K^+ concentration in section 2 of muscle with ischemic ST depression, as compared to section 3 of muscle with isoelectric ST segments from interinsular areas after bleeding.

In comparing intra- and extracellular ionic concentration in muscle specimen Nos. 2 and 3, a significant finding was the increase in gradient of both ions, especially of sodium, across the cell membrane in sample 2. In 9 of 11 cases, the sodium ionic gradient increased in ST depressed areas (with mean value larger than 14.5 mv, at 37°C, calculated in terms of membrane potential). In 7 of 11 cases the potassium ionic gradient increased in ST depressed areas (with mean value 3.4 mv, at 37°C, calculated in terms of membrane potential) (Table I).

6. A-V DIFFERENCE OF K AND NA IN ISCHEMIC CONDITIONS

The uptake of sodium and potassium ions by myocardium with ST depression then was determined by analysis of systemic arterial blood and coronary sinus blood. The ionic uptake was measured in myocardium with ischemic ST depression. The A-V ionic difference in the coronary circulation was used as an index of ionic uptake by myocardial cells. Potassium and sodium uptake was measured at several intervals for $^1/_2$ hour and compared with the values in the same dogs before inducing the ischemic condition. (Twelve experiments were performed.)

Potassium Uptake: Ischemia with ST depression ranging from 1 to 3 mm was associated with an increased uptake of potassium (0.3 to 1.9 meq/L above normal uptake).

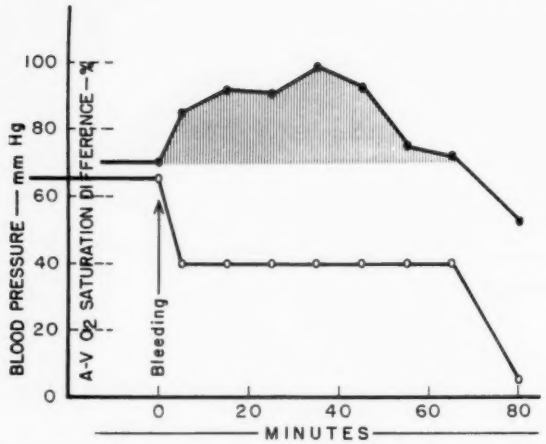


Fig. 5. Oxygen uptake by the heart during ischemia with ST depression. The oxygen uptake calculated by A-V oxygen difference increases with the duration of ischemia. After 35 minutes O_2 uptake decreases and in the terminal stage falls below normal values.

Sodium Uptake: There was no significant change in Na uptake in ischemia with ST depression. More, better-controlled experiments are needed.

7. OXYGEN DETERMINATIONS IN MYOCARDIUM IN ISCHEMIA WITH ST DEPRESSION OR ST ELEVATION

7A. Oxygen Saturation in Myocardial Venous Blood. In 10 dogs blood was sampled from the coronary sinus before and after inducing ischemia with ST depression by peripheral bleeding. Coronary sinus oxygen saturation before bleeding ranged from 25 to 30 per cent, but after bleeding fell to below 7 per cent. The oxygen saturation remained at this low level until just prior to the dog's death, when the blood from the coronary sinus changed visually from its dark, almost black, color to a more reddish hue. The fall in oxygen saturation of the coronary sinus blood is indicative of increased myocardial oxygen extraction in the ischemic myocardium with ST depression (Fig. 5).

In ischemia with ST segment elevation, due to ligation of a coronary artery, the oxygen saturation of the blood in the coronary vein corresponding to the ligated artery was extremely low when sampled one minute after ligation (less than 2 per cent saturation). Three to five minutes after ligation of the artery the oxygen saturation in the coronary vein blood increased remarkably to 40–50 per cent saturation. This saturation exceeded the normal saturation of coronary venous blood, which is 25–30 per cent.

In ischemia after ligation, the myocardial oxygen uptake seemed to increase sharply initially, then decreased below normal. The cells deprived of oxygen supply respond initially with an increased ability to extract oxygen available from the collaterals. Subsequently, with the establishment of severe cell damage, there is a great loss in O_2 extraction ability.

7B. Oxygen Tension in Myocardium. Preliminary studies were carried out to determine oxygen tension in myocardial segments giving rise to ST deviation. An improved oxygen meter was used for this study with a polarographic platinum oxygen electrode (Beckman model 221-PL). Ischemic areas of the myocardium with ST elevations were produced in 4 dogs by ligation of a coronary artery. Shortly after ligation the oxygen tension in these ischemic areas was markedly reduced in comparison to the oxygen tension in normal, nonischemic areas of the same heart. Similar observations have been made by Sayen *et al.*[4]

"Islands" of ST depression were produced in 6 dogs by bleeding. Oxygen tension was very low in these "islands" and in the areas between them. The oxygen tension in the "islands" of ST depression appeared equal in severity to that in the areas with ST elevation in the previous experiment. More determinations are being performed both in dogs and in human hearts at surgery.

8. FACTORS INFLUENCING ISCHEMIC ST DEVIATIONS

8A. Areas of ischemia with ST depression were produced in 3 dogs by lowering the mean blood pressure to 40 mm Hg. In one coronary artery, however, the blood pressure was maintained at normal level by artificial perfusion with the animal's own blood. "Islands" of ST segment depression appeared all over the myocardium with the exception of the area perfused by the artery with normal pressure where the ST segment remained almost isoelectric.

8B. In 5 dogs segments of coronary artery of various lengths were narrowed by external compression, and ischemia with ST depression was produced. This method was less consistent than bleeding in producing ST segment depression.

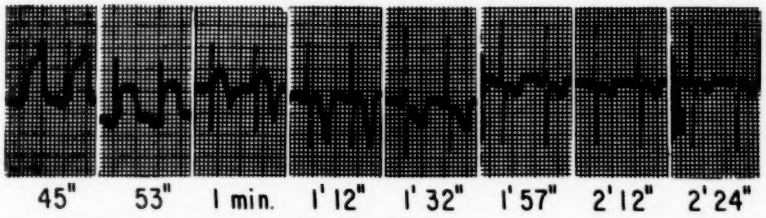


Fig. 6. Transient ST depression after ST elevation. On release of a ligature which had been on a coronary artery for 45 seconds, the elevated ST segment returns to the isoelectric line through a short intermediate phase of ST depression (1'32").

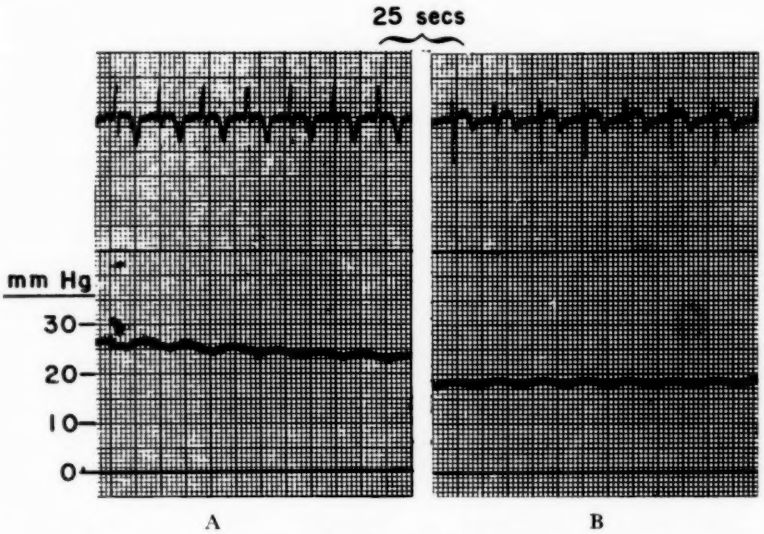


Fig. 7. Delay in appearance of ST elevation after ligation of coronary artery. (A) Ligation of a coronary artery results in immediate lowering of the wedge pressure in the corresponding coronary vein without apparent ECG change. (B) From the same continuous record as *A*. Fragment of continuous record shows delayed initial appearance of ST elevation. Delay in this case lasted 25 seconds. Wedge pressure remained remarkably high.

8C. Temporary ischemia with ST elevation was produced in 20 experiments by ligation of a coronary artery for about one minute. On release of the tie after one minute, the elevated ST segment returned to the isoelectric level gradually over the next one–two minutes. Transient ST segment depression appeared on occasion following ST elevation before this segment stabilized on the isoelectric line (Fig. 6). This transient reversal of ST displacement also was noted in the experiments with nonischemic ST displacement (experiment 9).

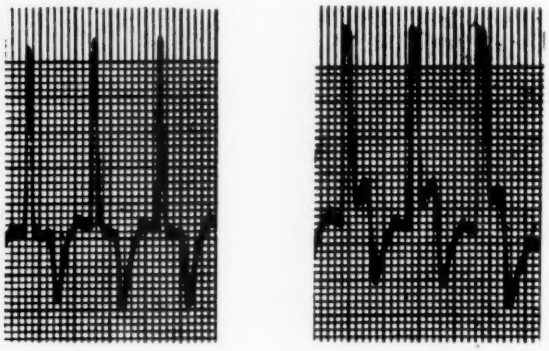
8D. Ischemia with ST elevation was produced by ligation of a coronary artery, with elevation of the ST segment appearing 25–35 seconds after ligation of the vessel (Fig. 7). The time lag between ligation and appearance of ST segment elevation was remarkably uniform in 30 dogs and was remarkably longer in comparison with that of nonischemic ST elevation observed in experiment 9.

During this initial 25–35 seconds the ST segment did not show depression in spite of ischemia, but remained isoelectric. Since the absence of ST depression could be explained by an absence of potassium migration into the cell due to deficient glucose supply, these experiments were repeated, injecting 5 per cent glucose solution (20 cc in 1 minute) into the coronary artery immediately after ligation. ST *depression* appeared within 1–2 seconds (Fig. 8), in contrast to those experiments in which glucose was not injected. This confirmed the concept that the entrance of potassium into the cell made possible

the electrical manifestation of ischemia with ST depression.

9. ST SEGMENT RESPONSE TO IONIC CONCENTRATION CHANGE IN EXTRACELLULAR MEDIUM IN NONISCHEMIC STATE

The findings on chemical analysis of the ischemic myocardium (as described in experiment 5) suggest that changes in ionic gradient may be partially responsible for ST segment deviation.



A B

Fig. 8. ST segment response to glucose perfusion after ligation of a coronary artery. (A) 5% glucose solution was injected distally into the coronary artery; ST depression occurs almost immediately in contrast to experiments without glucose injection, where ST was isoelectric initially. (B) ST segment elevation appears later.

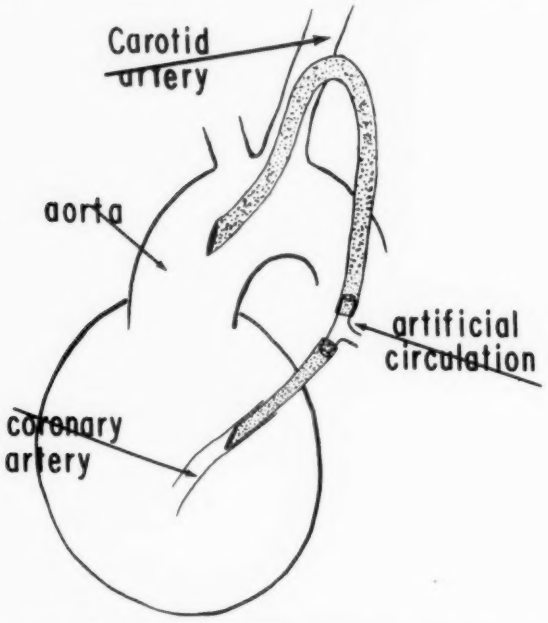


Fig. 9. Diagram illustrating the artificial coronary circuit. The carotid artery is connected to a major branch of a coronary artery through a plastic catheter.

Electrolyte distribution patterns similar to those found in ischemia with ST depression, as in classic angina pectoris, and ischemia with ST elevation, as in the variant form of angina and early myocardial infarction, were investigated in the following experiments. In the following experiments, however, ST segment elevation and depression were produced in *nonischemic* conditions.

An artificial coronary circuit was created that connected the carotid artery to a coronary artery (Fig. 9), and 5 cc of saline solution or solutions of sodium and potassium ions of various concentrations, all at body temperature, were injected into this artificial coronary artery circuit. The injections were repeated many times in each animal. After a certain number of injections, a state of persistent ST elevation occurred in most animals, and it was necessary to terminate the experiment. The point at which persistent ST elevation occurred varied widely in different animals. In some animals ST elevation persisted after repetition of the injection only a few times, while in others as many as ten injections failed to produce persistent ST elevation. It is to be emphasized that in all these experiments there was no ischemia.

A. Injection of High-concentration Sodium Solutions with 2 meq K/L. Saline solutions in concentrations of 0.9, 1.0, and 1.1 per cent (155, 171, and 188 meq/L of Na, respectively) were mixed with potassium to give a K concentration of 2 meq/L. Injection of these high-concentration sodium solutions into the artificial coronary artery circuit resulted in immediate ST segment *depression* in all 15 experiments. The ST depression became progressively more marked for 15–20 seconds, then on reaching its nadir gradually returned to the isoelectric line. The duration of the ST segment depression varied with the concentration of the solution, lasting from 10 seconds to 2 or 3 minutes after the nadir (Fig. 10). At the end of the period of ST segment depression, a short period of slight ST segment elevation occurred occasionally before return to the isoelectric line (Fig. 11).

Results consistent with the above were obtained with injections of hypertonic saline solutions mixed with blood or blood plasma from the same dog, provided the injections were made immediately after mixing the saline with the

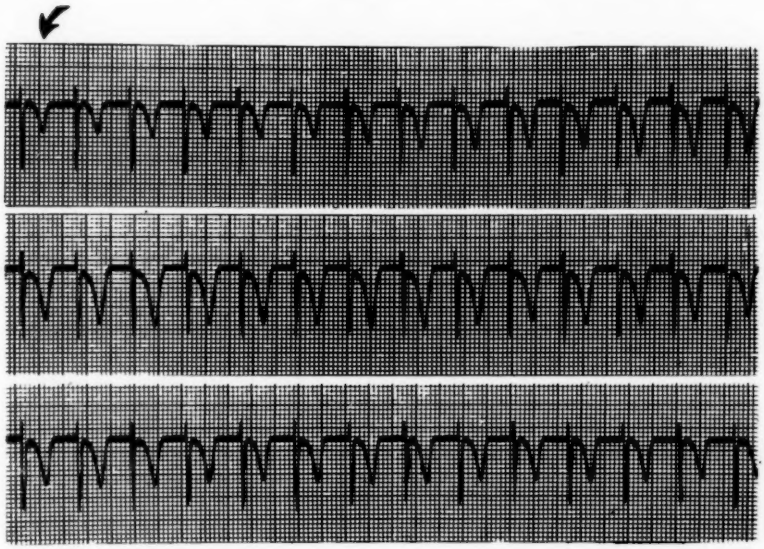


Fig. 10. ST segment response to perfusion (*arrow*) of hypertonic saline solution with 2 meq/L K^+ into coronary artery. The ST segment remains at almost same level. The T-P segment appears to elevate. The interpretation "ST depression" is relative to the T-P level.

blood. Injection of any of these solutions at a slow rate did not result in ST deviations. In any of these experiments if the electrolytes were mixed with blood or plasma and allowed to stand in the incubator for over $^1/_2$ hour before injection, no ST deviation occurred. This may be due to buffer action of the plasma or other unknown factors.

B. Injection of 0.8% Saline Solution with 2 meq K/L. Injection of 0.8% saline solution (136 meq Na/L) with 2 meq K/L into the coronary circuit did not change the ST segment, although the saline concentration was slightly less than normal.

C. Injection of Low-concentration Sodium Solutions with 2 meq K/L. Saline solutions of 0.7 and 0.6 per cent (119 and 103 meq Na/L, respectively) with 2 meq K/L were injected into the coronary circuit. The concentrations of these solutions, although less than normal, were above the threshold for hemolysis.

The ST segment became *elevated* immediately after injection of these solutions, and after reaching a peak gradually returned to initial levels (Fig. 12). The ST segment elevation persisted longer with the lower sodium concentration. Occasionally, slight transient ST segment depression appeared following ST elevation, before this segment stabilized on the isoelectric line.

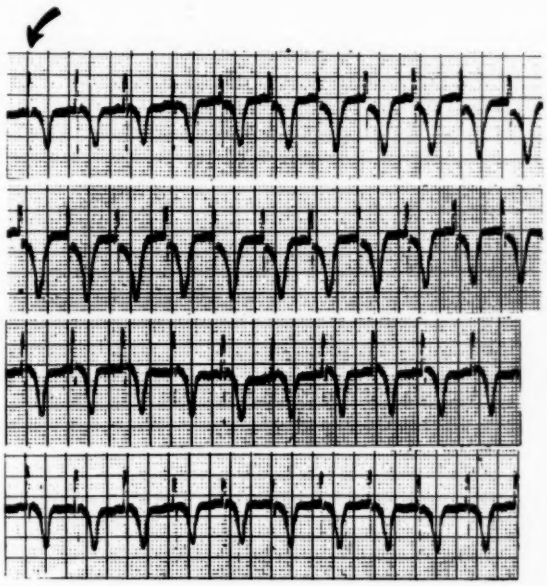


Fig. 11. ST segment response to perfusion (*arrow*) of hypertonic saline solution with 2 meq/L K^+ into a coronary artery. Slight transient ST elevation is seen following ST depression before return to the isoelectric line.

Injection of hypotonic sodium solutions mixed with blood or plasma from the same animal yielding a concentration of 116 meq Na/L were also injected into the coronary artery circuit.

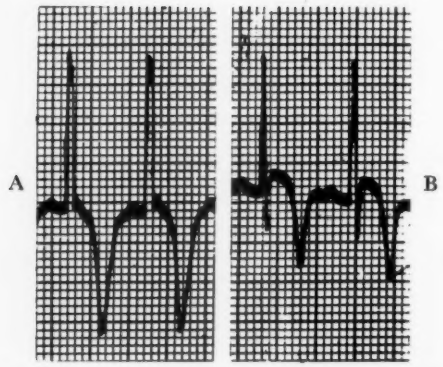


Fig. 12. ST segment response to perfusion of hypotonic saline solution with 2 meq/L K^+ into a coronary artery. (A) The control record shows an isoelectric ST segment. (B) ST segment elevation occurs with perfusion.

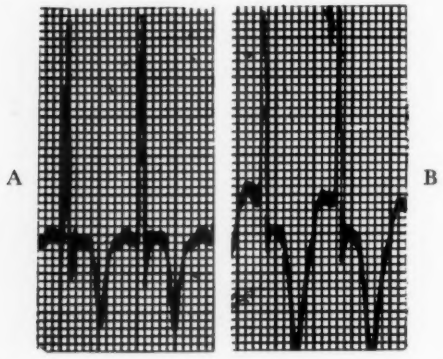


Fig. 13. ST segment response to perfusion of hypertonic saline solution without potassium. (A) Control record shows an isoelectric ST segment. (B) ST segment depression occurs with perfusion.

Results closely approximated those where blood or plasma mixtures were not used.

D. Injection of Hypertonic Sodium Solutions Without K. Hypertonic saline solutions without K were injected into the coronary artery circuit. ST *depression* was similar to that occurring with injection of hypertonic saline solution with 2 meq K/L (Fig. 13).

E. Injection of Low-concentration K Solutions in Normal Saline. Various concentrations of potassium chloride in 0.83 per cent saline (142 meq Na/L) were injected into the coronary artery circuit. With injection of 1 meq K/L solution ST *depression* occurred immediately, reaching its nadir in 15–20 seconds and returning gradually to the isoelectric line (Fig. 14). Sometimes slight transient ST segment elevation also appeared following ST depression. The duration of ST segment depression appeared longer than

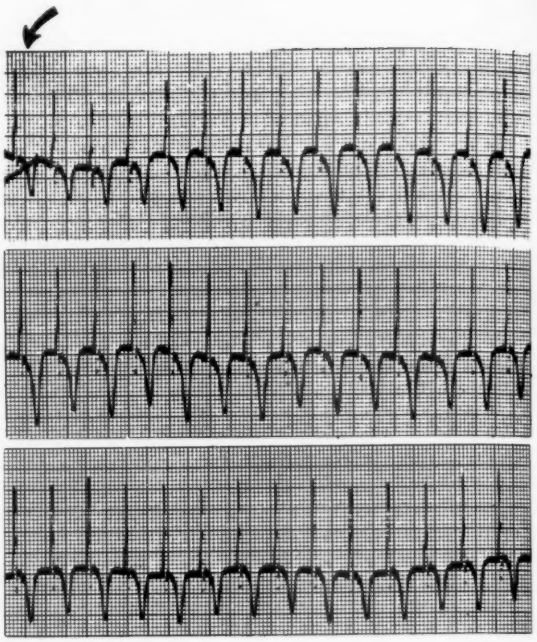


Fig. 14. ST segment response to perfusion (*arrow*) of low-concentration potassium solution (1 meq K^+/L) in saline solution (142 meq Na^+/L) into a coronary artery. ST depression occurs initially, followed by gradual return to the isoelectric line, then by slight transient ST elevation before return to the isoelectric line.

that caused with injection of hypertonic saline solution.

F. Injection of Higher Concentration K Solutions in Normal Saline. Injection of potassium solution in concentration of 3.8 meq/L or greater (i.e. above normal concentration) resulted in ST *elevation.* The ST elevation persisted longer than that caused by injection of hypotonic sodium solutions (Fig. 15).

It was noted in all parts of experiment 9 that the T-P segment deviation was predominantly responsible for ST segment deviation.

Changes in concentration of extracellular sodium ions (in terms of per cent change of ion) caused ST shifts *far greater* than those caused by corresponding per cent changes in concentration of potassium ions. ST deviation occurred with a change in sodium ionic concentration from 119 to 155 meq/L (0.7 to 0.9 per cent) or an equivalent of 7 mv in ionic membrane potential. ST deviation occurred with a change in potassium ion concentration from 3.8 to 1.0 meq/L or an equivalent of 36 mv in ionic membrane potential at 37°C (Fig. 16).

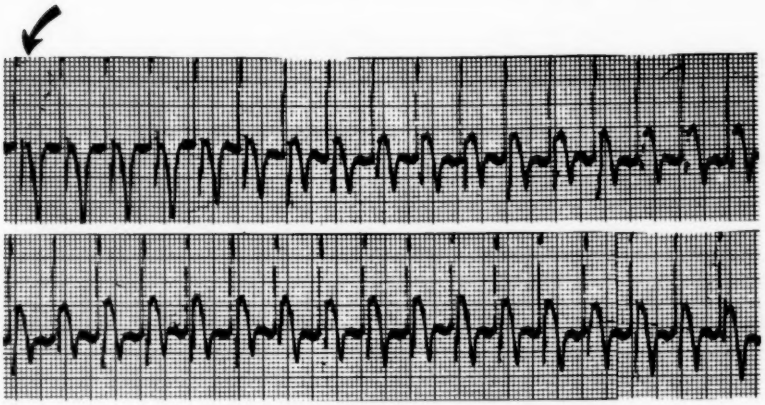


Fig. 15. ST segment response to perfusion (*arrow*) of high-concentration potassium solution (3.8 meq K^+/L) in saline solution (142 meq Na^+/L) into a coronary artery. ST elevation persists longer than ST deviations induced by various sodium solutions.

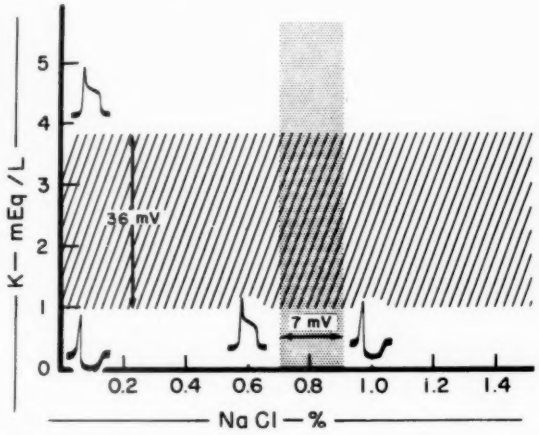


Fig. 16. ST segment response to sodium and potassium ionic concentration. The stippled area represents the range of extracellular sodium concentration without ST segment response (ST isoelectric). To the left of this range ST *elevates* with low sodium concentration. To the right ST *depresses* with high sodium concentration. The striped area represents the range of potassium concentration without ST segment response (ST isoelectric). Below this concentration range is the area of ST depression, and above this range, with high concentration of potassium ion, is the area of ST elevation.

Injecting different concentration of sodium and potassium apparently changes the ionic gradient between the extra- and intracellular compartments.

10. Injection of 5 per cent glucose

The close association of glucose with potassium in the metabolism of the heart prompted this experiment, in which 10 cc of 5 per cent (isotonic) glucose solution was injected rapidly into the

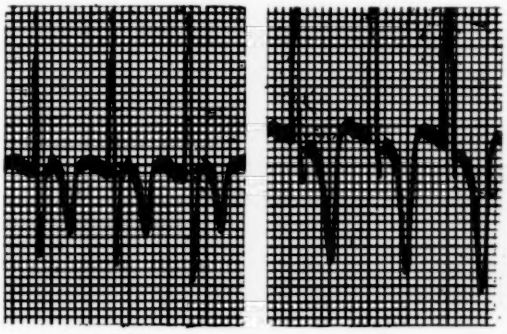


Fig. 17. ST segment response to injection of 5% glucose into coronary artery. (A) Control record with isoelectric ST segment. (B) ST depression occurs with glucose injection.

artificial coronary artery circuit in 10 dogs. ST segment *depression* resulted but apparently after an interval slightly longer than noted with the injection of electrolyte solutions (Fig. 17).

Discussion

Injury currents and ST deviations

Ionic Gradient Change and ST Segment Displacements. Classic electrocardiographic theory explains ST segment elevation on the basis of a decreased ability of the muscle cell membrane to depolarize and repolarize. ST elevation is regarded as an expression of injury currents.

Injury currents usually are classified into two types: injury current at rest or diastolic injury current, and injury current of activation or systolic injury current.[5,6]

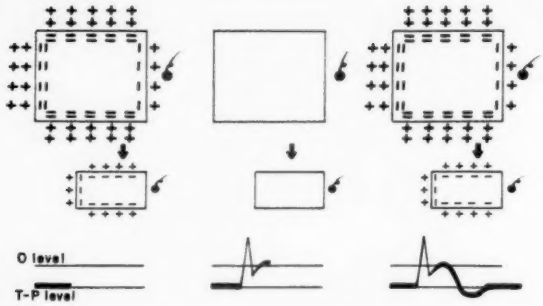


Fig. 18. Diastolic injury current. In this condition the injured membrane undergoes complete depolarization but is unable to achieve complete repolarization. A lead point facing an injured area, therefore, views the negative side of the equivalent double layer in the diastolic stage. This results in T-P segment depression. In the systolic stage there is no charge affecting the ST level which, therefore, remains at the zero level. This results in relative ST segment elevation as judged by the T-P level.

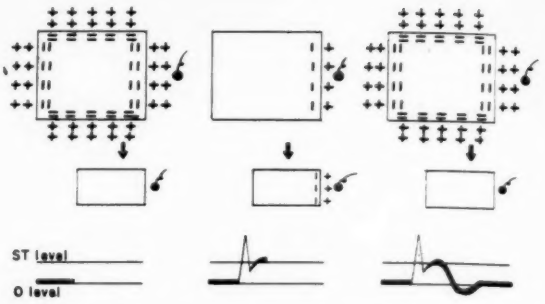


Fig. 19. Systolic injury current. In this condition the injured membrane is completely polarizable in the diastolic stage but unable to undergo complete depolarization. It remains, therefore, in a partially polarized condition during activation. A lead point facing the injured area views the positive side of its equivalent double layer in the systolic stage. It is not affected by any potential in the diastolic stage, since the closed double layer does not manifest a potential.

Injury Current at Rest or Diastolic Injury Current. With diastolic injury current, the injured muscle cell membrane supposedly loses the ability to maintain normal polarization or to repolarize to the level of normal polarization. The hypopolarization of the membrane in the resting state is manifest as a defect in the equivalent double layer (Fig. 18). This defect in the double layer causes T-P segment depression. Relative ST segment elevation is recorded therefore from a point facing the injured area.

Injury Current of Activation or Systolic Injury Current. With systolic injury current, the injured muscle membrane supposedly loses the normal ability to depolarize during activation and continues to carry charges of the electric double layer. This persistent double layer in the systolic stage gives rise to ST segment elevation in a point facing the injured area (Fig. 19). This incomplete depolarization has been called "active" ST elevation in contrast to the "passive" or relative ST elevation, previously described.

Both of these causes of ST segment elevation usually coexist and contribute to this shift. Both of these factors in ST elevation appear with the decrease of electrical membrane activity and may be expressed as "hypopolarization" and "hypodepolarization," respectively.

Primary Epicardial ST Depression. ST segment depression, by contrast, has been explained by "reciprocal" effects.[7,8] ST segment depression, in precordial leads in patients with classic angina pectoris, has been explained by the reciprocal effect of injury current in the subendocardial region. However, marked ST depression in direct epicardial leads without significant ST elevation in cavity and subendocardial leads has been noted on many occasions in this laboratory.[2] This ST depression cannot be explained in terms of reciprocal effect of injury current.

Injury current is explained in classic theory as already noted by assuming a decreased ability of the cell membrane for depolarization or polarization. It would seem reasonable, however, to postulate the opposite: an *increased* ability of the cell membrane for depolarization or polarization. Evidence to support such a concept may be found in a well-recognized phenomenon in the intracellular electrogram, increase in degree of "overshoot" and resting membrane potential. "Overshoot"[9,10] is a continuation of the process of depolarization ending in reversal of membrane polarization. The cell membrane thus temporarily has a reversed polarization, with the cell inside positive and the cell outside negative, as seen in Figure 20A.

After maximum reversed polarization has been reached, there is a gradual return to zero level, then a continuation of repolarization in the usual sense. This is demonstrated in Figure 20A where depolarization, polarization reversal, and repolarization display a monophasic curve. Generally, when the ionic sodium gradient across

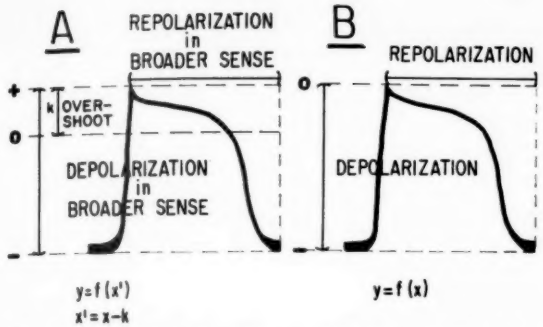


Fig. 20. Monophasic curves of injury current. (A) The actual intracellular lead electrogram demonstrating "overshoot." (B) The intracellular electrogram derived from classic theory.

the cell membrane increases, "overshoot" increases in magnitude; and when ionic potassium gradient increases, resting membrane potential also increases, and vice versa.[9,10]

Potential changes in the intracellular lead electrogram designed in accordance to classic membrane theory would also display a monophasic curve, as seen in Figure 20B. In this diagram, the configuration of the tracing is similar to that of the actual intracellular lead electrogram. The only difference from the actual intracellular electrogram is that the upstroke or depolarization ends at zero level.

If the configuration of the curves is the same, tracings A and B in Figure 20, even though different in the potential level of the upper part of the tracing, can be mathematically treated as the same function by transformation of coordinates. The upstroke of action potential in the actual intracellular lead can be correlated with the process of depolarization in classical membrane theory, and the succeeding portion, with the process of repolarization. The upstroke in the actual intracellular lead may be referred to as "depolarization in the broader sense," and the succeeding portion of action potential as "repolarization in the broader sense." If this concept is accepted, the meaning of "hyperpolarization" and "hyperdepolarization" will be clear.

If a portion of myocardium exhibits increased resting potential (as compared to the rest of the myocardium), it would be in a "hyperpolarized" condition. If a portion of myocardium exhibits more "overshoot" than the rest of the myocardium, it would be in a "hyperpolarized" condition. Increased polarization or depolarization

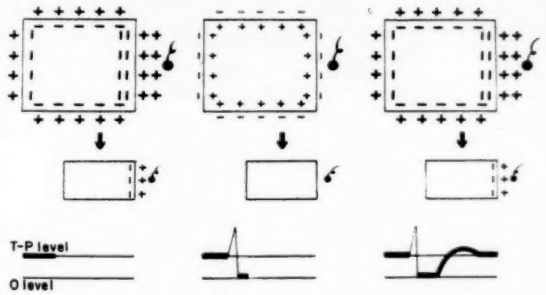


Fig. 21. Diastolic injury current with ST depression. The membrane undergoing injury in this condition is equally depolarizable with normal membrane. It is able to develop a hyperpolarization in the diastolic stage. A lead point facing the injured area, therefore, records a positive potential (T-P elevation) during diastole, but no potential in the fully depolarized condition. This results in a relative primary ST segment depression.

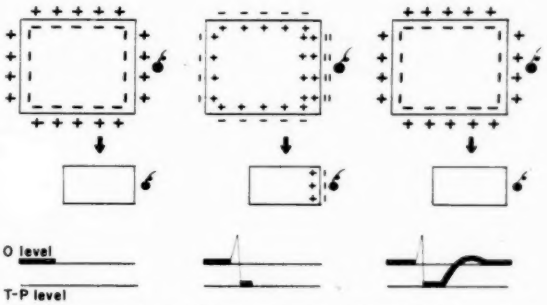


Fig. 22. Systolic injury current with ST depression. In the diastolic stage, the myocardium is uniformly polarized and there is no effective potential at the lead point facing the injured area. In the systolic stage, however, the injured area displays hyperdepolarization or greater polarization reversal and is reflected in the negative potential in that lead point. This results in active primary ST depression.

of the cell membrane would explain ST segment depression in epicardial leads without significant ST elevation in cavity or subendocardial leads. This explanation is offered as the cause of primary ST depression.

Diastolic Injury Current with ST Depression. With a hyperpolarized membrane, a lead point facing an area with increased ionic gradient at rest would have a positive potential at rest (Fig. 21). The T-P segment would be elevated, therefore, above the line of zero potential. If the muscle membrane underwent complete depolarization, zero potential would result and would be recorded as a line below the T-P segment. This line would represent the ST segment in a stage of complete depolarization.

Systolic Injury Current with ST Depression. If

hyperpolarization of the cell membrane is present at rest, a lead point facing this area would record a negative potential in the end stage of depolarization (Fig. 22). This hyperpolarization would result in active ST depression.

In both diastolic and systolic injury currents the ST segment depression is not reciprocal or secondary to ST elevation in another area. Electrolyte analysis of muscle specimens excised from areas with ST segment depression may be suggestive of increased polarization ability of the cell membrane in these ischemic areas. In experiment 5 the ionic gradient of sodium was increased greatly, while that of potassium was also increased, but to a considerably lesser degree.

In the intracellular electrogram, as reported by Weidman[9] and others,[10] the magnitude of the action potential upstroke varies with the concentration ratios of sodium and potassium in extra- and intracellular fluids. The steeper the ionic gradient, the larger is the magnitude of the action potential upstroke. Injection of hypertonic sodium solution into a coronary artery causes a transient increase in extracellular ionic sodium concentration. This results in an increased ionic sodium gradient.[9,10]

The increased ionic sodium gradient in this area might be expected to create a greater "overshoot" than is found in the areas with smaller ionic gradient. The ST segment would be displaced downward correspondingly, since this represents greater polarization reversal in the activation stage. Injection of high-concentration sodium solution extracellularly, therefore, should cause active ST depression. Injection of hypotonic sodium solution extracellularly, in contrast, might be expected to reduce the "overshoot," with consequent active ST elevation at a lead point facing the perfused area.

The ST deviations created by injection of potassium solutions were analogous but opposite to those with sodium. Potassium ions would appear to have an effect on resting membrane potential. An increase in ionic potassium gradient increases the resting membrane potential and vice versa. Potassium ion concentration, therefore, predominantly affects the resting membrane potential and brings about hyper- or hypopolarization.[11]

The mechanism of the electrical effect differs with sodium and potassium ions, although both ions increase the amplitude of the action potential through the ionic gradient. The injection of a less concentrated potassium solution increased the ionic potassium gradient, resulting in hyperpolarization with ST segment depression at a lead point facing the injected area. Injection of high-concentration potassium solutions, by contrast, results in ST segment elevation. Based on our experiments, injection of either high-concentration sodium or low-concentration potassium solutions led to ST segment depression which was caused indirectly by T-P segment elevation.* T-P segment depression after application of concentrated potassium citrate also has been found by Sodi-Pallares.[32]

These findings hypothetically suggest that ST depression in both cases was caused by local hyperpolarization of the injected area. The effect of potassium ions would seem to agree with this suggestion, whereas that of sodium ions would seem to disagree with this because it hypothetically lowers the ST segment due to hyperdepolarization. In the experiments with low-concentration sodium solution, ST segment elevation was also relative to the T-P level which was depressed, and active ST segment elevation was not detectable. This problem needs further investigation.

The great sensitivity of the T-P segment to undergo displacement with changes in extracellular sodium concentration also appears to be subject to some doubt. Proof is lacking that there is a direct dependence of ST segment deviation on sodium gradient change across the membrane. The value of 3.5 mv at 37°C, which expresses the difference between normal sodium level and threshold for T-P segment displacement, seems to be of insufficient magnitude to produce a 1–2 mv displacement of the T-P segment. This magnitude appears to be too small, as well, in comparison with the experimentally found values of muscle specimen analysis (experiment 5), or in comparison with the potassium value (36 mv at 37°C) necessary

* The existence of "active" ST segment depression was not clearly detectable because of the use of an R-C coupling amplifier in the electrocardiograph. An apparatus with direct-current amplifier will be utilized in the future to discern active ST segment depression.

to alter the T-P segment. The experiments with sodium reveal ST depression on the basis of T-P level deviation rather than active ST displacement, and this may be evidence against a direct effect of sodium on the membrane potential. Small changes in extracellular sodium ionic concentration, however, appear to contribute to resting membrane potential in an unknown manner.

ST Segment Depression "Without Reciprocity." The absence of significant reciprocity of the ST segment in cavity and subendocardial leads may be explained as follows: As a purely hypothetical example, assuming a hyperpolarized area in the subepicardium to be 1 cm in diameter and ventricular wall thickness as 1 cm, the solid angle value would be approximately 2 π on the epicardial surface and 0.21 π on the endocardial surface (Fig. 23). This means the reciprocal deviation on the endocardial surface would be about $^1/_{10}$ its magnitude at the affected subepicardial area. With pronounced epicardial ST depression the underlying cavity lead would reveal only $^1/_{10}$ reciprocal ST elevation. This would explain why pronounced ST segment elevation does not appear in cavity or subendocardial leads in the bleeding hypotensive animal experiments despite marked epicardial ST depression.

If epicardial ST depression was reciprocal to subendocardial injury current, the subendocardial ST elevation, on a mathematical basis, should far exceed the epicardial ST depression. A 3 mm epicardial ST depression would be reciprocal to a 30 mm ST subendocardial elevation (a 1:10 ratio). Injury currents in the subendocardium in actuality are small[33] and this militates strongly on a mathematical basis against the occurrence of such a reciprocal effect. Epicardial ST segment depression in these experiments would appear to be primary to a disorder of subepicardial muscle characterized by an abnormally increased polarization ability.

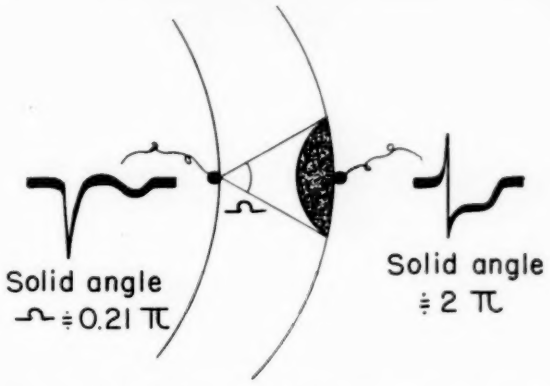


Fig. 23. Primary epicardial ST depression. There is a hyperpolarized area in the subepicardium giving ST depression in the epicardial lead. There is barely visible reciprocal ST elevation in the subendocardial or cavity level, because the reciprocal ST elevation is only $^1/_{10}$ of the primary ST depression.

MYOCARDIAL METABOLISM AND ST CHANGES

Some Clinical Implications of Ionic Gradient Change. Local changes in electrolytes and ionic gradient produce ST elevation or depression experimentally in animals in nonischemic conditions, and may play an important role in producing ST displacement in some clinical cases. Abnormal cell metabolism may lead to hyper- and hypopolarization of the cell membrane. It is remarkable that muscle undergoing "ischemia" presents two different and opposite electrocardiographic responses: ST segment *depression* and ST *elevation*. It would seem in general that when ischemia is not severe, ST depression occurs, and when it is severe, as in coronary occlusion, ST elevation occurs. These ischemic conditions, therefore, for the purpose of simplicity are referred to as "ischemia with ST depression," and "ischemia with ST elevation."

Experiments are now in progress to determine why some types of ischemia cause ST elevation and others ST depression. Ischemia with ST elevation would appear to be more severe in degree, since it results generally from complete occlusion of a coronary artery. The occurrence of both ST depression and ST elevation in ischemia may be explained in terms of differences of cell metabolism and energy production which occur in this condition. Ischemia, meaning deficient coronary blood flow, decreases all supplies necessary for the cells, including the supply of oxygen.[34] In ischemic conditions the myocardial metabolism greatly differs from the normal metabolism as to glucose, potassium, and undoubtedly other aspects.

Normal Myocardial Metabolism. Most energy for heart contraction comes from glycogen derived from blood glucose. Normally, glycogen

passes through several metabolic stages, finally being broken down to CO_2 and water. Glycogen breakdown has two different phases which are consecutive under normal conditions.

First phase: Anaerobic breakdown of glycogen. Glycogen breaks down through glucose to pyruvic acid. Only $^1/_{10}$ of the total energy is derived from this anaerobic breakdown.

Second phase: Aerobic breakdown of glycogen. This phase is supposed to begin with pyruvic acid entering into the Krebs (tricarboxylic acid) cycle and ending with the final products of glycogen breakdown, carbon dioxide and water. This aerobic breakdown yields $^9/_{10}$ of the total energy. The bulk of energy for heart contraction thus is derived from the aerobic phase of glycogen breakdown.[12,13]

The intense intolerance of the heart to oxygen lack is due to this dependence on the presence of oxygen for the overwhelming majority of its energy.

Myocardial Metabolism in Ischemic Conditions. In ischemia with ST depression, aerobic breakdown is limited by oxygen lack.[12,13] The degree of suppression of aerobic metabolism varies with the degree of hypoxia. With decreased aerobic breakdown of glycogen, energy from this process decreases. To meet the demand for energy, increased anaerobic breakdown is necessary.[14] Since the energy yield from this phase of glycogen breakdown is low, it must increase markedly to compensate for the loss of energy through aerobic breakdown.

Myocardial cells thus rapidly reducing their glycogen reserves[15] would tend to restore their depot and meet the demand for energy by increasing glucose uptake from the extracellular compartment.[16] There is a well-known cooperation between glucose and potassium uptake by the cell, in that glucose does not enter the cell independent of potassium.[17–21] Potassium therefore plays an important part in carbohydrate and energy metabolism.[22–24]

In ischemia with ST depression (experiment 6), an increased uptake of potassium by the myocardial cells was found in all 12 dogs, varying from one to eight times normal. In another experimental series with ST depression (experiment 5), the potassium concentration of the myocardium of the ST depressed area was higher than that of an isoelectric ST area or of normal myocardium (prior to hypotension) (see Table I). This suggests that under the conditions of the experiment, myocardial cell metabolism in an area of ischemia with ST depression is different from myocardial cell metabolism in an area with isoelectric ST segment. Cell metabolism in the area with isoelectric ST segment, under the conditions of the experiment, also may be different from cell metabolism in normal cells not subjected to the conditions of this experiment. The significant finding, however, is that metabolism of the myocardium in the ST depressed area is different from that of the ST isoelectric area.

The reason for the difference in metabolic action in different parts of the muscle is not yet established. It may be due to local changes in blood supply subject to unknown factors. The increase in intracellular potassium changes the ratio of concentration between intra- and extracellular fluid. Increase in ionic potassium gradient seems to bring ST depression as noted in these experiments and in the foregoing discussion. The response of the cell metabolism to the ischemia which is manifest by ST depression is in conformity with Cannon's theory of homeostasis. In terms of this concept ST depression in classic angina pectoris would indicate the appearance of a defense mechanism which renders the cell better prepared to meet the hazards of more severe ischemia. The cell membrane also appears to alter rapidly its intra- and extracellular components as a protective mechanism.

In ischemia with ST depression, the lack of oxygen supply has resulted in increase in the uptake of glucose and potassium by the cells from the extracellular compartment. Oxygen lack and increased glucose uptake indirectly affect the cationic gradient. Oxygen lack alone, without sufficient glucose and potassium in the extracellular compartment, would not be able to produce ST depression. It was noted in experiment 8D that extreme oxygen lack from ligation of a branch of the anterior descending coronary artery did not produce ST depression immediately unless 5 % glucose solution was injected into this coronary artery at the same time. It was found in experiment 10 that injection of 5 % (isotonic) glucose solution into the cor-

onary circuit without limiting oxygen supply also induced ST depression. These experiments suggest that injection of glucose in concentration far above normal blood level probably stimulates the cells to increased glucose and potassium uptake. In the treatment of uremic patients by infusion of 20% glucose solution, ST segment depression has been recorded.

When ischemia is extreme and the anaerobic energy production does not meet the demand for energy, myocardial cells undergo injury or ischemia with ST elevation. In this severe ischemia the cell membrane loses its ability to some degree to maintain the cationic gradient between intra- and extracellular fluid.[25] If this ischemia remains permanent or lasts too long, then the function of cell membrane will be destroyed. Intracellular potassium leaves the cell[26,27,28] and the potassium ionic gradient across the cell membrane decreases. In ischemia with ST elevation, sodium ions from the extracellular fluid also enter the cell and decrease the sodium ionic gradient across the cell membrane, as noted by Kardesch *et al.*[25] In ischemia with ST elevation, decrease in the ionic gradients of both potassium and sodium contributes to ST elevation. It is possible that ischemia with ST depression may not be generally as severe as ischemia with ST elevation.

In experimental bleeding and the classic type of angina pectoris, some parts of the myocardium develop ischemia with ST depression, owing to insufficient blood supply from depression of blood pressure or narrowing of the coronary arteries. In the variant form of angina pectoris, ischemia with ST elevation develops because of the severe deficiency of blood supplied from one coronary artery. If the artery becomes thrombosed myocardial infarction develops, but if adequate blood supply is restored, as in most cases of the variant form of angina, before they develop thrombosis, the ST elevation will disappear.[1,2] This would explain the electrocardiographic changes in the variant form of angina pectoris.[1,2] If adequate blood supply is restored following ischemia with ST elevation, the myocardium may increase its uptake of glucose and consequently of potassium. This may account for the transient ST depression which appeared in experiment 8C.

A clinical case of the variant form of angina demonstrating these phenomena was observed in this laboratory. A man, aged 49, with typical variant form of angina, developed marked ST elevation which was recorded in a lead at the umbilical level (Fig. 24). This was indicative of posterior and postero-inferior ischemia. The ST was elevated for about four minutes during the period of severe pain. As the pain gradually subsided and disappeared over a two-minute period, the ST elevation diminished. Then without settling at the isoelectric line, the ST became depressed 1 mm for about one minute. It then returned gradually to the isoelectric line over a period of two and one-half minutes. The same transient ST elevation also was reported by Wolferth *et al.*[29]

NONISCHEMIC ST DEPRESSION

There are clinical conditions associated with ST depression other than ischemia of angina pectoris. In the animal experiments nonischemic ST deviation was produced by perfusion under various conditions. A clinical example is to be found in diabetic coma where large amounts of insulin and saline have been given. This transient ST depression probably reflects an altered ionic membrane gradient due

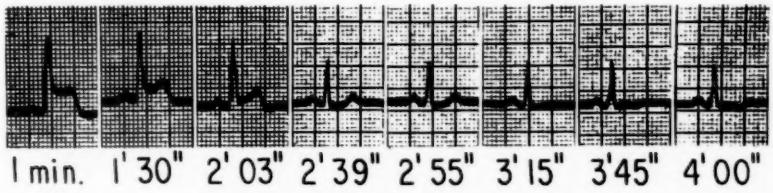


Fig. 24. Selected complexes of a continuous tracing recorded from a patient during an attack of the variant form of angina pectoris. For 2 minutes ST elevation is present. This is followed by brief period of ST depression and later a return to isoelectric line. The same observation has been made in the dog following release of a coronary artery ligature (Fig. 6). This suggests that attacks of the variant form of angina pectoris are due to hypertonus of an arteriosclerotic artery.

to increased uptake of glucose and potassium.[30]

In such noncardiac conditions as familial periodic paralysis, serum potassium concentration is decreased during the attack of paralysis. Potassium migrates from the extracellular space into the cells. Danowski, Elkin, *et al.* also observed reciprocal transfer of sodium in one case. It is believed that familial periodic paralysis is connected with a metabolic fault which favors the movement of potassium from the extra- to the intracellular compartment.[31] The well-recognized ST depression which occurs during attacks of this condition may be explained as well by the alteration in cationic intra-extracellular gradient.

There are undoubtedly other noncardiac conditions which give rise to primary ST segment elevation and depression. This is undoubtedly also true for certain drugs.

Summary

The experimental data here reported indicate that ST deviation is related largely to a change in the balance between intra- and extracellular electrolytes. This change in intra- and extracellular electrolyte balance occurs in ischemic heart disease as well as in a wide variety of noncardiac conditions.

Acknowledgments

The authors wish to express their gratitude to Drs. Naci Bor and Takashi Wada for their help on experiments 1, 2, and 7B; and to thank Drs. Wilfried Mommaerts and Hideo Watanabe for their assistance.

The chemical determinations were performed by the Bio-Science Laboratories, Los Angeles, to whom we are most grateful.

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The Effect of Molar Sodium Lactate in Quinidine Intoxication

An Experimental Study*

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QUINIDINE† is widely used in the therapy of various cardiac arrhythmias. It has been well documented that in certain disturbances of cardiac conduction and rhythmicity, such as bundle branch block and heart block, the use of quinidine is relatively contraindicated.[1,2] While untoward effects are not common,[3–5] quinidine intoxication may present a serious therapeutic problem. There is no specific method for reversing toxic clinical and electrocardiographic effects other than discontinuing the drug and allowing for its metabolic dissipation. This study was instituted in view of the efficacy of molar sodium lactate‡ in narrowing previously widened QRS complexes of various etiologies[6,7] (e.g., hyperpotassemia) and because of the observation that several of the electrocardiographic changes of quinidine intoxication resemble those of uremia with hyperpotassemia.[8–10] The purpose of this paper is to report our observations on the effect of molar sodium lactate in quinidine intoxication in the experimental animal.

METHOD AND MATERIALS

Twenty mongrel dogs weighing between 7.2 and 9.7 kg were used in this study. The dogs were anesthetized with intravenous pentobarbital sodium. Endotracheal intubation was performed and the animals were maintained on an artificial respirator with oxygen. The femoral vein and artery were cannulated; the artery was used for continuous blood pressure recordings and for determinations of blood pH, serum electrolytes, and chemistries. The vein was utilized for the administration of the various parenteral solutions. Electrocardiograms (standard lead II) were recorded as a control and, subsequently, throughout the experiment. The blood pressure was recorded on the Sanborn Twin Visocardiette, utilizing the femoral artery cannula connected to a Sanborn manometer.

Approximately twenty mg (17.8 to 21.0) of quinidine hydrochloride/min, representing a dose of 2.1–2.9 mg/kg/min, was given intravenously until various cardiotoxic effects were observed. In the dog the lethal dose of quinidine has previously been determined to be 60 to 200 mg per kg when administered at a rate of 1 to 4 mg/kg/min.[11] A total of 20 to 180 ml of molar sodium lactate was then given intravenously at a rate of 3 to 10 ml/min and the effects on the electrocardiogram, blood pressure, blood pH, serum electrolytes and chemistries were observed.

Control blood pH, serum sodium, potassium, calcium, magnesium, chlorides, phosphorus and plasma bicarbonate were determined utilizing standard laboratory procedures.[12–17] In addition to the control specimen, blood samples were obtained immediately after cessation of intravenous quinidine, immediately after giving molar sodium lactate, and 15 to 20 min following the administration of molar sodium lactate.

RESULTS

The data obtained from both the control and experimental animals were carefully analyzed as follows:

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† The injectable quinidine hydrochloride used in this study was supplied through the courtesy of Brewer and Company, Inc., Worcester, Massachusetts.

‡ The molar sodium lactate was kindly supplied by Eli Lilly and Company, Indianapolis, Indiana.

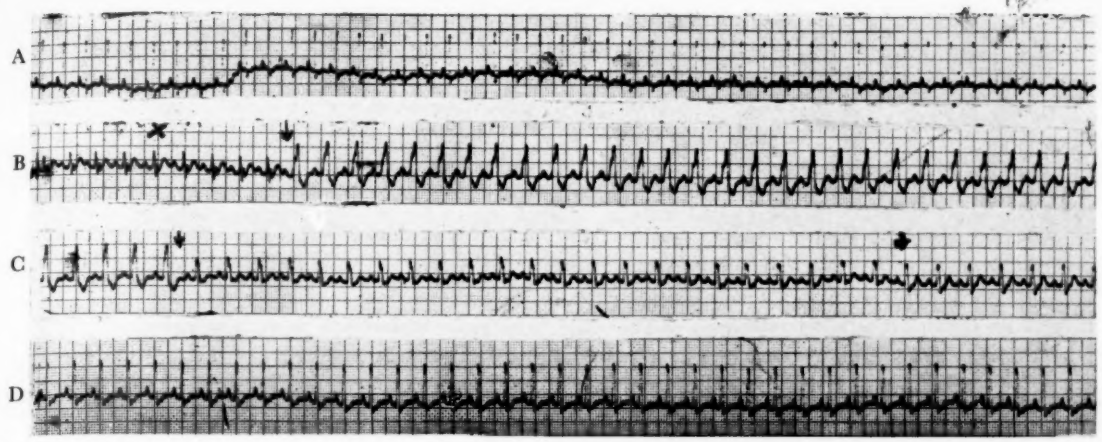

Fig. 1. Effects of molar sodium lactate on reversible quinidine intoxication. (A) Control tracing (lead II). (B) Quinidine stopped at *x* after 350 mg were given. Note spontaneous change in QRS configuration (at arrow). Heart rate decreased from control of 188/min to 140/min. The QRS complexes widened from 0.03 to 0.12 sec; and the PR interval lengthened from 0.12 to 0.14 sec. (C) First arrow indicates changes seen after 10 ml of intravenous molar sodium lactate given in 45 sec. Heart rate is now 125/min. The QRS complexes have narrowed to 0.08 sec; there is no change in the PR interval. (D) Ten minutes after a total of 20 ml of molar sodium lactate the QRS complexes measure 0.06; the heart rate is 150/min and the PR interval is 0.12. The record closely resembles the control ECG.

Electrocardiographic Changes: (*1*) *Reversible Changes:* With the administration of quinidine an initial increase in the heart rate associated with RS-T segment depression was observed. Prolongation of the QT interval with gradual slowing of the heart rate and further RS-T segment depression followed. Control upright or inverted T waves early became inverted or upright, respectively, and the QRS complexes subsequently progressively widened (most often resembling the pattern of left bundle branch block). The P waves increased in width and in amplitude and the PR interval gradually widened from a control ranging between 0.08 and 0.12 sec to 0.12 to 0.21 sec. These were reversible changes observed in all dogs.

In nine animals studied at this reversible stage of quinidine intoxication, the dosage of quinidine was 29.5 to 36.8 mg/kg; the total dosage ranged from 280 to 350 mg. In this group the QRS complexes widened from 0.06 to 0.12 sec above the control. Within two minutes after starting the intravenous infusion of molar sodium lactate, there was narrowing of the widened QRS complexes from 0.10 to 0.12 to 0.06 sec. Subsequently, the RS-T segment depression gradually became less marked and the previously inverted T waves became upright. The deep S waves gradually disappeared. The PR interval slowly returned to the control duration and the P waves were restored to normal amplitude and duration. The total time required to return to a normal or near normal electrocardiogram following treatment with intravenous molar sodium lactate was from 4 to 20 min (Figs. 1 and 2).

In four control animals observed in a reversible stage of toxicity, the dosage of quinidine was 35 mg/kg; the total dosage ranged from 320 to 340 mg. After stopping the quinidine there was a return to a normal or near normal electrocardiogram in 30 to 35 min (Fig. 3).

(*2*) *Irreversible Changes:* Irreversible changes in our animals, consistent with previously reported studies,[18–20] were characterized by periods of sinoauricular arrest followed by nodal escape beats which generally progressed within several minutes to A-V nodal rhythm. Auriculoventricular dissociation with a lower nodal or a high idioventricular rhythm (usually very slow) was observed in seven dogs as a severe cardiotoxic effect of quinidine. The dosage of quinidine was between 30.5 and 62.5 mg/kg with a total dose of 200 to 500 mg.

In these animals infusion of molar sodium lactate resulted in a transient return to normal sinus rhythm with narrowing of the QRS complexes followed by marked sinus or nodal bradycardia terminating in ventricular standstill or fibrillation (Fig. 4). This very slow

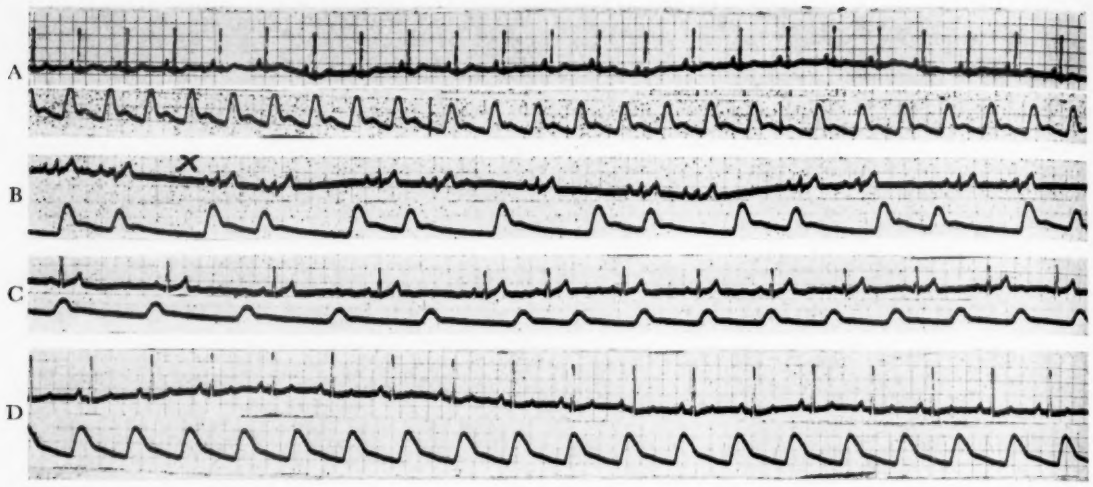

Fig. 2. Effect of molar sodium lactate on reversible quinidine intoxication. (A) Control tracing (lead II). The blood pressure and electrocardiogram were recorded on two machines. (B) Quinidine was stopped at *x* after 500 mg intravenously in 25 min. The rate has slowed from 97 to 57 per min; the blood pressure has dropped from 85/36 to 56/12. The QRS complexes have widened from 0.04 to 0.10 sec and the PR interval has increased from 0.12 to 0.16 sec. (C) Thirty seconds after injection of 10 ml of molar sodium lactate. The rate is 50/min; the QRS complexes have narrowed to 0.06 sec and the PR interval has decreased to 0.14 sec. Sinus pauses were abolished. (D) Five minutes after 20 ml of molar sodium lactate. The blood pressure was 60/16, the heart rate has increased to 75/min; the QRS complexes measure 0.04 sec and the PR interval is 0.14 sec. The ECG now resembles the control record.

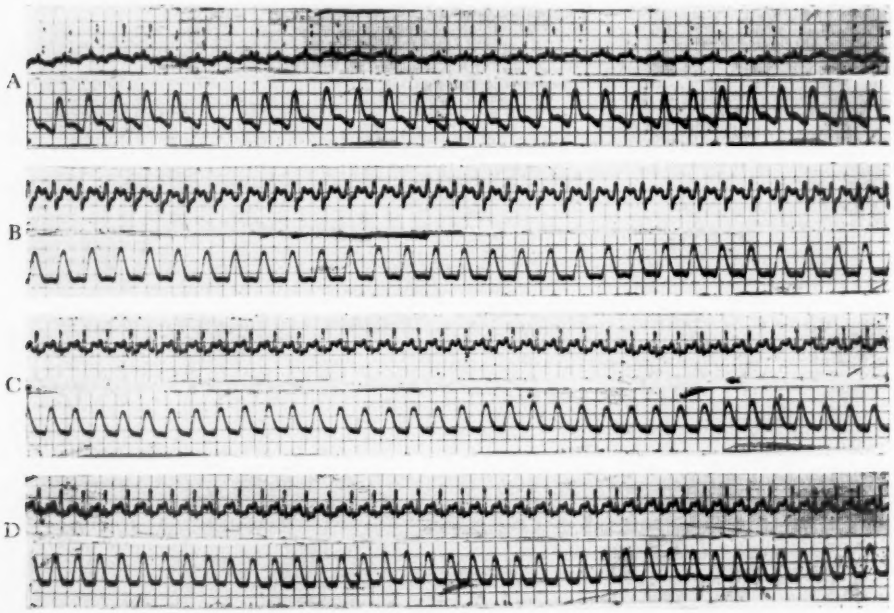

Fig. 3. Prolonged effects of intravenous quinidine in an untreated animal. (A) Control tracing (lead II): Blood pressure 116/90 (BP and ECG were recorded on two machines). (B) After 520 mg of quinidine intravenously in 26 min. Blood pressure 96/74. There have been no changes in the heart rate. The PR interval has increased from 0.12 to 0.16, and there is widening of the QRS complexes from 0.06 to 0.12 sec. A deep S wave is present. (C) Twenty-two minutes after cessation of the quinidine infusion: Blood pressure 98/76. The heart rate remains 150/min. The P wave is broadened and notched. The PR interval has returned to the control duration, but the QRS complex is still widened to 0.10 sec. The S wave is less prominent. (D) Forty minutes after stopping the quinidine: Blood pressure 100/80. There is no essential change from the previous tracing and QRS and P wave abnormalities are still present.

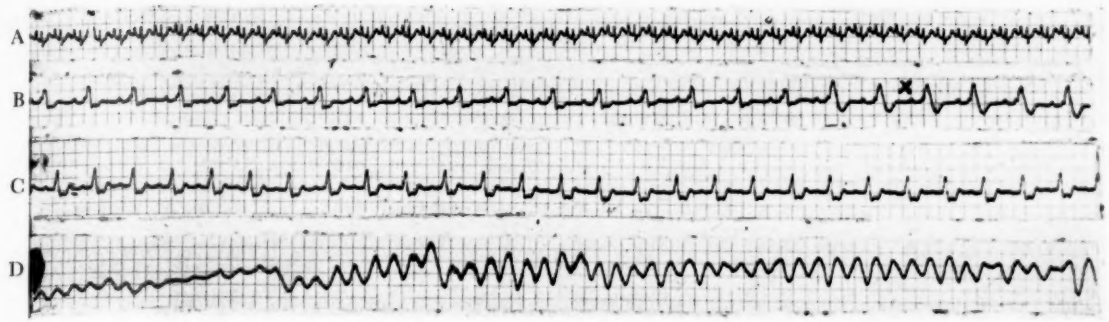

Fig. 4. Irreversible stage of quinidine toxicity terminating in ventricular fibrillation. (A) Control tracing (lead II) with a heart rate of 176/min. (B) After 500 mg the quinidine hydrochloride was stopped at *x*. The ventricular rate decreased from 176 to 79/min, the QRS complexes widened from 0.05 to 0.22 sec, and the PR interval increased from 0.10 sec control to 0.20 sec. (C) Following 40 ml of molar sodium lactate given in 4 min, there was transient narrowing of the QRS complexes and an increase in the ventricular rate from 79 to 100/min. The ST segment depression became more marked. (D) Four minutes after molar sodium lactate was stopped the animal developed ventricular fibrillation.

heart rate could not be speeded by intravenous or intracardiac adrenalin or isopropylnorepinephrine (Isuprel).

Mechanism of Death: Of the seven animals that died, ventricular fibrillation was the terminal cardiac mechanism in five and ventricular standstill occurred in two.

Blood Pressure: A decrease in blood pressure uniformly accompanied the electrocardiographic manifestations of quinidine intoxication. This fall in blood pressure was greatest where the signs of quinidine intoxication were most marked. Marked blood pressure changes and electrocardiographic abnormalities were not significantly improved by molar sodium lactate. In animals with less severe quinidine intoxication the blood pressure was restored to normal levels coincident with the return of the electrocardiogram to a normal configuration. In several animals a decrease in pulse pressure preceded the electrocardiographic evidence of early quinidine intoxication.

pH, Electrolytes and Chemistries: There were no significant changes in the serum sodium, potassium, chloride, calcium, phosphorus and magnesium obtained immediately after quinidine administration, immediately after cessation of sodium lactate therapy and during the 15- to 20-min period of observation following the molar sodium lactate infusion. The arterial blood pH and plasma bicarbonate, however, showed a significant decrease following the administration of intravenous quinidine with a return to prequinidine levels within 15 min after the intravenous administration of molar sodium lactate. The blood pH showed a mean decrease of 0.13 with a range of 0.05 to 0.22. The mean decrease in plasma bicarbonate was 2.3 meq/*l* with a range of 1.2 to 4.5 meq. The pH of the quinidine sulfate employed in this study was 7.03. Using 7 per cent of total body weight of the dogs for determining the blood volume, an in vitro study was performed using equivalent amounts of injectable quinidine hydrochloride and dog's blood. In six samples the mean decrease in blood pH was 0.08.

Discussion

The precise biochemical effects of quinidine in both therapeutic and toxic doses are still unknown. It has been suggested that electrolyte alterations in cardiac muscle may be the cause of quinidine intoxication: an increase in myocardial potassium has been observed in the experimental animal following the injection of quinidine.[21] One of the effects of quinidine appears to be an alteration in the flow of sodium and potassium ions within the heart muscle.[21] It is therefore of clinical interest that a similarity has been observed between the electrocardiographic findings in uremia with hyperpotassemia and those in quinidine intoxication.[8,9,10,21]

It has been reported that quinidine in minute amounts can inhibit the uptake of glucose and fructose prior to that phase of carbohydrate metabolism in which these two sugars and glycogen share a similar metabolic pathway.[22] A decrease in the glucose tolerance test following

quinidine therapy has been reported by other investigators.[22] Abramson and co-worker[23] pointed out that injected lactate acts like an easily oxidizable substrate which replaces other foodstuffs in metabolism. Bing *et al.*[24] found that the isolated dog's heart removed from the circulating blood more lactic acid than any other substance and that the lactate serves directly as an energy source. An increase in arterial lactate levels caused an increase in myocardial lactate extraction. If quinidine significantly inhibits the uptake of glucose and fructose for metabolic use, as previously reported, then lactate may alleviate quinidine intoxication by directly entering the oxidative mill of the Krebs cycle to improve the function of the cardiac cell.

Korns,[18] Linenthal *et al.*,[19,20] and Cheng[25] and co-workers in previous studies have outlined the electrocardiographic changes of quinidine intoxication which are similar to our findings. They are characterized by sinoauricular slowing, followed by sinus pauses, sinus arrhythmia, marked QRS widening, and RS-T and T wave changes. Intraauricular conduction defects leading to partial or complete intraauricular block have been observed. The objective manifestations of moderate quinidine intoxication measured were rapidly reversed to pre-quinidine levels by intravenous molar sodium lactate. Molar sodium lactate does not appear to alter the ultimate fate of animals severely poisoned with quinidine. Disappearance of sinoauricular rhythm with the appearance of A-V nodal rhythm appears to represent an irreversible stage of quinidine intoxication in the experimental animal, terminating in ventricular standstill or fibrillation. It is our preliminary impression, however, that a priming dose of molar sodium lactate administered before giving the quinidine may delay or entirely prevent this irreversible toxic manifestation.

A decrease in the systolic and diastolic blood pressure was observed in all animals studied and generally coincided with the earlier electrocardiographic manifestations of quinidine intoxication.

From the laboratory determinations it appears that a metabolic acidosis follows the administration of intravenous quinidine hydrochloride. This change in pH was reproduced in vitro by the addition of quinidine hydrochloride to dog's blood in equivalent amounts proportional to those used in the intact animal. In all of the animals this metabolic acidosis was corrected. Recent work by Campbell and associates[26] suggests that acidosis may be a factor in the production of hypotension. By preventing or correcting this with sodium lactate the toxic effects of quinidine may be significantly delayed.

Studies are in progress to determine in patients if the therapeutic effects of quinidine are altered by reversing early toxic manifestations with the administration of intravenous molar sodium lactate.

Summary

Quinidine is widely used in the therapy of various cardiac arrhythmias. Toxic effects, while well documented, are relatively uncommon. Contraindications to the use of quinidine have, however, limited clinical application.

Quinidine depresses cardiac rhythmicity and conduction. This appears to be a direct effect on the myocardium, with little if any effect being mediated through the autonomic nervous system. At the present time there is no method of therapy which will reverse cardiotoxic quinidine effects.

Molar sodium lactate appears to promptly reverse moderately severe cardiotoxic electrocardiographic effects, and to correct the hypotension secondary to quinidine intoxication, restoring the blood pressure to normotensive levels. These preliminary observations suggest that molar sodium lactate may be effective clinically in treating quinidine intoxication in man.

Serum electrolyte and pH determinations revealed that the animals developed a moderately severe acidosis which was promptly restored to normal by molar sodium lactate.

The possible mechanisms of action are discussed.

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Clinical Studies

Ventricular Tachycardia

With Particular Consideration of Digitalis Therapy*

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VENTRICULAR tachycardia is one of the less common but more serious cardiac arrhythmias. The first demonstration of this abnormal mechanism on the electrocardiogram was made by Sir Thomas Lewis a half-century ago.[1] In a review of the cases from the Boston City Hospital, Williams and Ellis[2] found an incidence of ventricular tachycardia of 1 in each 1,800 electrocardiograms taken. In general, the prognosis in this condition reflects that of the underlying heart disease. Since it is most often associated with serious coronary artery disease and particularly myocardial infarction, the over-all outlook is ominous. When it occurs without other evidence of heart disease, the prognosis is favorable.[3] The clinical picture produced by the tachycardia may vary from no symptoms at all to the picture of profound, catastrophic collapse.

The records of the cases of ventricular tachycardia seen at the John Gaston Hospital during the ten years 1947 to 1956, inclusive, have been reviewed. In general the experience at this hospital parallels that of previously reported series. However, certain aspects of this experience, and in particular certain individual case histories, are of interest. We are reporting briefly the findings in this group of cases and presenting case reports of two of the cases. The question of therapy in ventricular tachycardia will be dealt with in more detail in the discussion below.

CASE MATERIAL

Twenty-two cases with electrocardiographic study were assigned the discharge diagnosis of ventricular tachycardia during the interval reviewed. Three cases have been discarded because review of the electrocardiograms did not confirm the diagnosis. This left 19 cases to be reported. These cases do not represent the total experience with this condition at the John Gaston Hospital during the study period. Not included are cases with this clinical diagnosis but in which electrocardiograms were not obtained, usually because of the demise of the patient very soon after onset of the arrhythmia. It is also thought that a certain number of cases with short runs of essentially asymptomatic ventricular tachycardia diagnosed by the electrocardiogram have been missed by virtue of not having been signed out with that diagnosis, since the arrhythmia was not a prominent part of the clinical picture. In addition 17 cases from this hospital of ventricular tachycardia due to digitalis toxicity occurring during a 17-year period, which included the ten years of this report, have been reported elsewhere by von Capellar *et al.*[4] Their cases are not included here. The majority of their cases were those in which runs of paroxysmal ventricular tachycardia occurred in the presence of multiple disturbances of the cardiac mechanism. In general, the clinical manifestations of the tachycardia per se

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TABLE I
"Catastrophic" Arrhythmias

CASE	AGE	SEX	ETIOLOGY OF HEART DISEASE	CLINICAL PICTURE	CHARACTER OF ARRHYTHMIA	TREATMENT OF ARRHYTHMIA	RESULTS OF TREATMENT	COURSE
1	51	M	No evidence ht. disease other than arrhythmia	Recurrent syncopal attacks with convulsions	Recurrent long runs of ventricular tachycardia	Procaine amide followed by quinidine	Converted to normal rhythm	Followed 3 months. No recurrence.
2	37	F	Hypertensive cardiovascular disease	Severe syncopal attacks. On maintenance digitalis	Recurtent runs of ventricular tachycardia	Procaine amide	No response	Died - Autopsy: 1-Arteriolar nephrosclerosis 2-Coronary atherosclerosis
3*	47	F	Acute myocardial infarction due to arteriosclerotic heart disease	3 1 2 weeks post-infarction developed sudden, profound and persistent shock. Mild diabetes mellitus	Persistent(20 hrs.) ventricular tachycardia	Quinidine, procaine amide, magnesium sulfate, sedatives, and Lanatoside C	No response until given IV Lanatoside C. Then converted.	Followed 3 years. No recurrence of arrhythmia
5	83	M	Arteriosclerotic heart disease	Sudden onset severe dyspnea nausea and vomiting and shock	Ventricular tachycardia	Procaine amide	No response	Died- No autopsy
6	83	F	Arteriosclerotic heart disease	Severe dyspnea, chest pain, cyanosis and collapse	Ventricular tachycardia	Procaine amide	No response	Died - Autopsy: 1-Coronary atherosclerosis 2-Interstitial myocardial fibrosis especially of septum. No recent infarct. 3-Situs inversus
10	72	F	Arteriosclerotic heart disease	Stokes-Adams attacks due to paroxysms of ventircular tachycardia	Complete AV block with idioventricular rhythm and runs of paroxysmal ventricular fibrillation	Procaine amide	No response	Died- Autopsy: Coronary atherosclerosis with marked involvement of septal vessel.
13*	50	M	Arteriosclerotic heart disease with old infarction	Palpitation,weakness, dyspnea, nausea and vomiting	Persistent ventricular tachycardia (3 days)	Quinidine and Procaine amide	No response	Died - Autopsy: 1-Old myocardial infarction 2-Congential absence left kidney
19	61	F	Arteriosclerotic heart disease	Stokes-Adams attacks with syncope and convulsions associated with runs of ventricular tachycardia	Complete heart block with idioventricular rhythm and runs of ventricular tachycardia and flutter	Procaine amide and quinidine	No response procaine amide. Controlled on quinidine	No follow-up after discharge

* Reported in detail in body of article.

were not readily separable from the over-all manifestations of digitalis intoxication.

Clinical Findings

Etiology of Heart Disease: The pertinent clinical data in this series of 19 cases are summarized in Tables I–III. The underlying heart disease was overwhelmingly arteriosclerotic heart disease. Sixteen cases were considered to have that diagnosis. Four of these 16 patients had had proved recent or remote myocardial infarction, and two others probably suffered infarctions. Two cases had hypertensive cardiovascular disease. In one case there was no evidence of heart disease other than the arrhythmia. The over-all mortality was 12 (63 per cent). In six of these autopsies were performed. Death was thought to be directly due to failure to control the arrhythmia in five cases (cases 2, 5, 6, 10, and 13).

Symptoms: In eight cases (Table I) the onset of the arrhythmia and severe symptoms associated with it was the major clinical problem at the time of admission or became so later with onset of the arrhythmia. In nine cases (Table II) it was difficult to assign symptoms to the arrhythmia per se in that it consisted of paroxysms of ventricular tachycardia (often in association with multiple arrhythmias) in the presence of advanced heart disease. Two cases (Table III) were difficult to classify into one or the other of the above groups.

Digitalis as a Factor: Seven patients were on maintenance digitalis at the time of onset of ventricular tachycardia. In only one case (case 17) was it thought that digitalis intoxication might have contributed to development of the arrhythmia. It is notable that only one of the eight cases in which the arrhythmia per se was the major problem had previously received

TABLE II

Arrhythmias as "Incidental" Finding in Severe Heart Disease

CASE	AGE	SEX	ETIOLOGY OF HEART DISEASE	CLINICAL PICTURE	CHARACTER OF ARRHYTHMIA	TREATMENT OF ARRHYTHMIA	RESULTS OF TREATMENT	COURSE
4	65	M	Arteriosclerotic heart disease two months postinfarction	Congestive heart failure, abdominal pain, substernal pain. On digitalis	Multiple arrhythmias plus runs of ventricular tachycardia	Quinidine and procaine amide	Control of runs of tachycardia	Died--No autopsy
7	71	M	Arteriosclerotic heart disease. Probable myocardial infarction.	Uncontrolled heart failure with multiple arrhythmias. On maintenance digitalis	Multiple arrhythmias with runs of ventricular tachycardia	Quinidine	Ventricular tachycardia controlled	Died--no autopsy
9	71	F	Arteriosclerotic heart disease	Uncontrolled long standing congestive heart failure. On maintenance digitalis	Multiple arrhythmias with runs of ventricular tachycardia	Quinidine and procaine amide	Ventricular tachycardia controlled but complete AV dissociation appeared.	Died- Autopsy: Generalized and coronary atherosclerosis. Myocardial fibrosis
11	62	F	Arteriosclerotic heart disease	Uncontrolled long standing congestive heart failure. On maintenance digitalis	1st degree AV block, multifocal ventricular prematures, runs of ventricular tachycardia	Quinidine (0.2 Gm. single oral dose)	Ventricular tachycardia ceased prior to dose of quinidine	Died--No autopsy
12	66	M	Arteriosclerotic heart disease	Congestive heart failure and ventricular tachycardia	Ventricular tachycardia	Digitalis	Rhythm converted to normal	Follow-up one month. No further trouble.
15	67	M	Arteriosclerotic heart disease	Congestive heart failure	Multiple arrhythmias with runs of ventricular tachycardia	Quinidine Procaine amide and digitalis	No response	Died--No autopsy
16	57	F	Hypertensive cardiovascular disease	Ventricular tachycardia due to quinidine given for atrial fibrillation. On digitalis until 3 days prior to admission.	Atrial fibrillation. Runs of ventricular tachycardia	Quinidine withheld	Ventricular tachycardia ceased	Followed two years. No further trouble.
17	71	M	Arteriosclerotic heart disease	Chronic congestive heart failure. On maintenance digitalis. Given 1/2 of digitalizing dose in addition. Probable digitalis toxicity.	Chaotic rhythm with runs of ventricular tachycardia	Quinidine	Ventricular tachycardia ceased	Died--No autopsy
18	60	M	Arteriosclerotic heart disease. Acute myocardial infarction	Acute posterior myocardial infarction	Ventricular tachycardia	Quinidine	Rhythm converted to normal	18 months follow-up. No further trouble.

digitalis. One patient (case 16) was thought to have developed ventricular tachycardia due to quinidine toxicity, the quinidine having been given in an attempt to convert atrial fibrillation.

Treatment and Results: Four patients were treated with procaine amide. None of the four converted to a normal rhythm and all four died. However, the dosage was clearly inadequate in one case and relatively low in the other three. Six patients were treated with quinidine. In five patients the ventricular tachycardia disappeared after quinidine. Three of these patients died later of progression of their underlying disease. The sixth patient (case 11) received a single dose of quinidine 0.2 Gm orally which was not repeated when it was found that the runs of ventricular tachycardia had already subsided. She later had a sudden convulsion and died. The immediate cause of death was not determined.

Five patients received both quinidine and Pronestyl either together or in sequence. In three patients this resulted in control of the arrhythmia. One of these three died later of progression of his heart failure. In the fourth patient the runs of ventricular tachycardia ceased, but complete A-V dissociation appeared and the patient died. The fifth patient (case 13 reported below) did not respond to quinidine and procaine amide and died with the tachycardia persisting.

Two patients received quinidine, Pronestyl, and digitalis. In one case there was no response and death ensued. In the other case (case 3 reported below) there was apparent response to digitalis after failure of quinidine and Pronestyl to convert the rhythm to normal. One

TABLE III
Unclassified Cases

CASE	AGE	SEX	ETIOLOGY OF HEART DISEASE	CLINICAL PICTURE	CHARACTER OF ARRHYTHMIA	TREATMENT OF ARRHYTHMIA	RESULTS OF TREATMENT	COURSE
8	72	F	Arteriosclerotic heart disease. Diabetes mellitus.	Diabetic coma. Ventricular tachycardia	Ventricular tachycardia	Quinidine	Converted to sinus rhythm	Died-Autopsy: Generalized and coronary atherosclerosis
14	78	M	Arteriosclerotic heart disease probable old myocardial infarction	Episodes of cyanosis and dyspnea associated with paroxysms of tachycardia	Atrial fibrillation with runs of ventricular tachycardia	Quinidine	Converted to sinus rhythm	Later required digitalis for congestive heart failure. 3 months follow-up.

patient (case 12) who was in obvious congestive heart failure with paroxysmal ventricular tachycardia at a rate of 180/min was treated with digitalis alone with conversion to normal rhythm and remission of the symptoms of failure. The remaining case which is the one in which toxicity to quinidine was thought to have produced the tachycardia was treated by withdrawing quinidine, with resultant disappearance of the tachycardia.

Case Histories

The following cases are reported in detail because they are thought to be of especial interest.

Case 3. E. G., a 47-year-old Negro female, was admitted to the John Gaston Hospital on March 3, 1954, because of chest pain. She had had diabetes mellitus since 1952, but had never required insulin. An electrocardiogram taken in 1953 had been normal (Fig. 1). On physical examination the temperature was 98°F, pulse 116, respiration 24, and blood pressure 140/118. She was obese and in moderate distress. The heart tones were muffled. Laboratory studies included blood sugar 390 mg %, CO_2 21 meq/*l*, white blood count 13,000, erythrocyte sedimentation rate 22 mm/hr, urine sugar 4+, and VDRL positive in a dilution of 1 to 4. The electrocardiogram revealed typical changes of acute anterolateral myocardial infarction (Fig. 1).

The patient was treated with bed rest, morphine, insulin, and anticoagulants. She was quite ill for the first few days, but by the second week was asymptomatic. She appeared to be making an uneventful recovery when on March 28, 1954, almost four weeks after admission, she suddenly fainted and had a mild generalized convulsion followed by nausea, vomiting, chest pain, and profound shock. She was cold, clammy, and a rapid apical pulse was noted. The blood pressure at first was 60/40 and then became unobtainable. The radial pulse was imperceptible. An electrocardiogram revealed ventricular tachycardia at a rate of approximately 280/min (Fig. 1). Severe shock persisted for 20 hours. She was given Demerol and oxygen.

During the first nine hours of the tachycardia she was given quinidine gluconate, 24 gr intramuscularly plus 3 gr orally. Procaine amide, 900 mg, was then given intravenously during a period of $1^1/_2$ hours. She then received magnesium sulfate, 10 cc of 10 per cent solution intravenously two times. In addition she had been given morphine, paraldehyde, and barbiturates. There was no response of the tachycardia to any of the above.

Eighteen and one-half hours after onset of the tachycardia, she was given Cedilanid (lanatoside C) 0.4 mg intravenously. This was repeated in 45 minutes and again 45 minutes after that. Immediately after the third dose of Cedilanid, she converted to normal sinus rhythm (Fig. 1). This was approximately nine hours after the last dose of quinidine and approximately six hours after the last dose of procaine amide. Her subsequent hospital course was uneventful. She was discharged from the hospital on April 26, 1954. She has been followed in the clinic to date without further serious difficulty. A recent electrocardiogram is also shown in Figure 1.

Case 13. R. B., a 50-year-old white male, was admitted to the John Gaston Hospital on February 20, 1952, because of palpitation, perspiration, weakness, dyspnea, and nausea of 12 hours' duration. His temperature was 97°F, blood pressure 100/70, respirations 22, and apical pulse rate 220. He was moderately dyspneic, apprehensive, and appeared ill. There was a grade 2 apical systolic murmur. His past history revealed that he had had an acute posterior myocardial infarction in July, 1951, from which he had made an uneventful recovery. On December 31, 1951, he had had an attack of paroxysmal ventricular tachycardia which had ceased after 24 hours following treatment with intramuscular quinidine and intravenous procaine amide. Three weeks later he had a second attack of ventricular tachycardia which lasted seven days and finally reverted to sinus rhythm after 0.8 Gm of quinidine intravenously. He had been on maintenance procaine amide since that time.

His electrocardiogram on this admission again revealed ventricular tachycardia with a rate of 220/min. Routine laboratory studies of blood and urine were normal. During the first several hours he was given moderate doses of quinidine intramuscularly and intravenously with no response. He was then given procaine amide, 1 Gm intravenously. The QRS interval signifi-

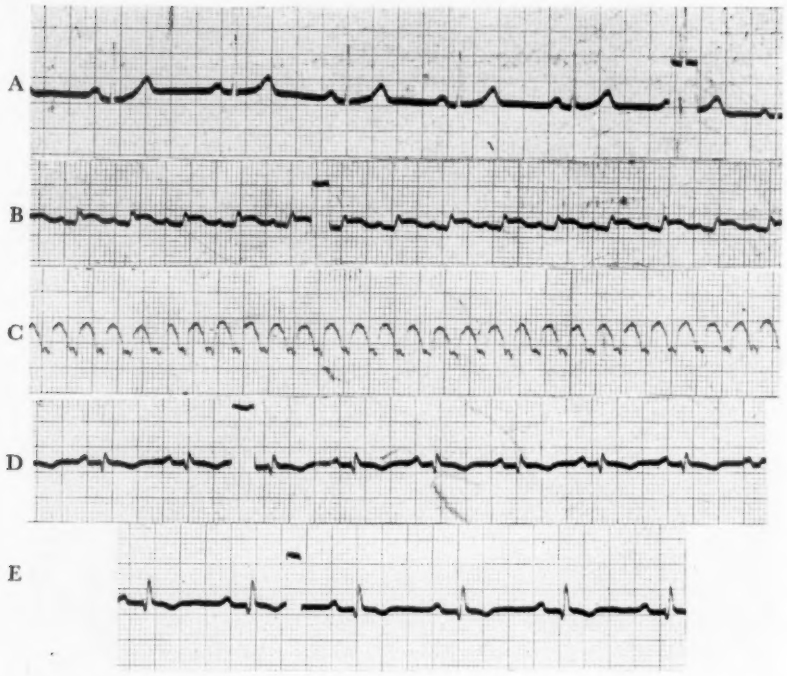

Fig. 1. Sample electrocardiograms (lead 1) in case 3. (A) March 24, 1953. (B) March 5, 1954, showing changes of acute anterior infarction. (C) March 28, 1954, showing ventricular tachycardia, rate 280. (D) March 31, 1954, following reversion of rhythm to normal. (E) April 2, 1957.

cantly widened after this and the rate fell from 220/ to 150/minute, but the abnormal mechanism persisted. During the next 48 hours repeated attempts were made to break the abnormal rhythm with gradually increasing doses of quinidine. On February 21, 1 Gm potassium chloride in 1,000 cc solution was given intravenously with no response. His general condition gradually worsened, with progressive weakness, cyanosis, mental confusion, and persistence of the tachycardia at a rate varying from 150 to 220/min. On February 23, 1952, he was given 0.8 Gm quinidine gluconate intravenously. Five minutes following completion of this, he had a rapid progressive fall in rate from 180 to 60 to 30 to 0 with death following.

Autopsy revealed generalized atherosclerosis with marked coronary atherosclerosis, cardiomegaly, and an old myocardial infarction involving the apical, lateral, and inferior portions of the left ventricle. There was no evidence of recent infarction. An incidental finding was congenital absence of the left kidney, left ureter, and left renal vessels.

Interesting Features of Other Cases: Certain other cases present features worthy of brief mention. Case 19 was given first Pronestyl and then quinidine for Stokes-Adams attacks due to paroxysms of ventricular tachycardia and flutter in the presence of complete A-V block. Both drugs are contraindicated in such a situation.[3] However, in this instance no bad effects resulted, and in fact the attacks were controlled or else ceased spontaneously following the administration of quinidine. Case 10 presented interesting anatomic findings at autopsy. The clinical story was that of complete A-V block with Stokes-Adams attacks due to paroxysmal ventricular tachycardia and death probably due to ventricular fibrillation. The autopsy revealed atheromatous degeneration of a septal vessel with very minimal coronary sclerosis elsewhere. Case 1 was the single case without evidence of heart disease other than the arrhythmia. This patient showed a good response to procaine amide with continued control on maintenance quinidine.

Discussion

The problem of therapy in ventricular tachycardia is not a simple one. The outlook at best is apt to be treacherous, with prognosis poor regardless of treatment. The condition is not common, and the difficulty of setting up controlled series of observations is obvious. Fur-

thermore, the attacks of tachycardia may subside spontaneously without specific treatment, so it is never possible to be certain that the treatment employed was actually responsible for the favorable result.

The currently accepted treatment is the use of quinidine or procaine amide.[3] If the arrhythmia is due to digitalis intoxication, potassium salts are indicated.[3] Digitalis has been generally considered as not only useless but dangerous in this condition.[5–7] Especially in the presence of acute myocardial infarction or advanced organic heart disease, digitalis has been considered to be contraindicated.[8,9]

Is Digitalis Dangerous in Ventricular Tachycardia?: The injunction against digitalis seems to be based on two considerations. The first rests on the concept, not entirely uncontroversial, that digitalis increases myocardial excitability or irritability[10,20] and therefore would predispose to aggravate further a tendency to ectopic mechanisms. However, the effect may actually be one of increasing automaticity of the ventricle rather than excitability.[10] Conversely, quinidine or procaine amide, by decreasing myocardial excitability, would tend to abolish ventricular ectopic mechanisms.[3,11] The second consideration militating against digitalis is the observation that toxic doses of digitalis may give rise to ventricular tachycardia and subsequently to ventricular fibrillation.[9,12–14] Indeed this is generally considered to be the ultimate effect of digitalis toxicity.[9] However, it should be pointed out that this second objection to the use of digitalis may be applied with equal force to quinidine and procaine amide. Both of these drugs in toxic doses may give rise to ventricular tachycardia and ventricular fibrillation.[3,11]

Reported Experiences with Digitalis: In spite of the above objections digitalis has been used from time to time in the treatment of ventricular tachycardia without ill effect and at times with apparently efficacious results. Scott[15] in 1921 used digitalis without evident harmful effect in a case of ventricular tachycardia and achieved partial control of the attacks with it. Foster and Thayer[16] used full digitalizing doses to the point of nausea without ill effects in a case of persistent ventricular tachycardia. It is not clear, however, whether it was beneficial since the attack ceased the day following cessation of the drug because of nausea. In 1950 Gilson and Schemm[17] reported the use of digitalis for ventricular tachycardia in the presence of acute myocardial infarction. In three of the four instances they reported the patient had already been previously digitalized and was on maintenance digitalis. In spite of this they administered full digitalizing doses with conversion of the arrhythmia to normal and marked clinical improvement of the patient in every case. It was their impression that congestive heart failure was associated with the tachycardia in all of their cases.

Shapiro *et al.*[18] reported on the use of intravenous Cedilanid (lanatoside C) in several cases of ventricular tachycardia not associated with acute myocardial infarction or digitalis toxicity. They found its use effective and not dangerous in their cases. They point out that Pronestyl and quinidine are not entirely innocuous drugs. Houghton and Frank[19] used digitalis in cases after failure of procaine amide and quinidine and had some successful conversions of rhythm to normal. They also used it in the presence of acute myocardial infarction without ill effect.

Lown and Levine[20] describe a case in which ventricular tachycardia with collapse developed following mitral commissurotomy. The patient was already on maintenance digitalis. After no response was obtained to Pronestyl, quinidine, or KCl the patient was given ouabain with conversion back to his previous atrial fibrillation and disappearance of all signs of ventricular irritability.

Digitalis in Authors' Cases: Case 3 which we have reported is an example of a profoundly shocking attack of ventricular tachycardia which persisted for 20 hours and ceased following intravenous Cedilanid (lanatoside C) after quinidine and procaine amide had failed to effect conversion. Case 13 is very similar in that quinidine and procaine amide failed to convert a persistent tachycardia. The patient died from the effects of the arrhythmia. One cannot help but speculate on what effect digitalis might have had if used. Case 12 (not reported in detail) in this series was a patient in congestive heart failure with paroxysmal ventricular tachycardia which was treated with digitalis alone,

with conversion of rhythm and relief of failure.

These experiences plus those reported by others suggest that the injunction against the use of digitalis in ventricular arrhythmias has perhaps been too stringent. It would seem reasonable that in cases of ventricular tachycardia not due to digitalis toxicity, and especially if procaine amide and quinidine have failed, digitalis should be given a trial. Whether or not there is any theoretic basis for its effectiveness in the absence of some degree of concomitant congestive heart failure the fact remains that at times it has appeared to be efficacious.

One other characteristic of ventricular tachycardia that this small series points up is the frequency with which the arrhythmia itself in contradistinction to the underlying heart disease may present as a catastrophic clinical problem. In eight of these cases (see Table I) the arrhythmia produced disastrous symptoms. Control of the arrhythmia resulted in marked clinical improvement in three. Failure to control the arrhythmia resulted in death in the other five. There were two other cases (see Table III) in which the arrhythmia per se probably contributed to a major portion of the symptomatology.

Summary

Nineteen cases of ventricular tachycardia have been reviewed. The catastrophic character of the arrhythmia was impressive in eight cases (42 per cent). The question of therapy has been discussed with particular reference to the place of digitalis in the treatment of this arrhythmia. In cases of ventricular tachycardia not due to digitalis toxicity, digitalis merits a trial especially if procaine amide and quinidine have failed.

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Restoration of Sinus Rhythm in Experimental and Clinical Ventricular Arrhythmias by Methoxamine Hydrochloride*

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MYOCARDIAL infarction accompanied by hypotension (shock) has a high mortality rate. Both the hypotension and mortality are greatly increased if arrhythmias are also present. Corday and co-workers[1] have shown that coronary artery flow is reduced 15 per cent by premature ventricular systole and 60 per cent by ventricular tachycardia. In some instances the elimination of a rapid ectopic rhythm will of itself relieve the shock state.

At the present time, treatment of cardiogenic shock with vasopressor drugs is an established procedure.[2–8] However, the opinion has been expressed that "all the sympathomimetic amines in sufficiently large doses will produce ectopic rhythms."[2] It is thus important that the vasopressor-sympathomimetic drug chosen for use in cardiogenic shock should be one with the least potential for provoking cardiac arrhythmias. Still more desirable would be a pressor amine that has intrinsic antiarrhythmic properties.

In previous studies[9] using dogs, we reported that Vasoxyl† could prevent ventricular tachycardia resulting from epinephrine injected during cyclopropane anesthesia, and ventricular fibrillation arising from epinephrine administered during chloroform inhalation.

The plan for the present study was twofold: (1) To test Vasoxyl in dogs in which ventricular arrhythmias were established by a variety of experimental procedures designed to represent as closely as possible clinical ventricular arrhythmias of various etiologies. (2) To try the drug in patients with ventricular arrhythmias arising in various clinical states corresponding to those produced experimentally in the dog.

VASOXYL STUDIES ON VENTRICULAR ARRHYTHMIAS IN DOGS

(1) *Myocardial Infarcts:* Myocardial injury and necrosis was produced in 15 anesthetized dogs to mimic clinical myocardial infarcts accompanied by ventricular arrhythmias. Two procedures were used: ligation of the left anterior coronary descending artery, just distal to the bifurcation of the circumflex branch;[10] and the injection, through the intact chest, of a freshly prepared suspension of zinc hydroxide into the left ventricular wall.[11] Following coronary ligation, ectopic beats arose from variable ventricular foci, appeared at irregular intervals and were coupled or existed as short bursts of ventricular tachycardia; the premature ventricular systoles constituted 28 to 44 per cent of the heart beats. Single injections of 2 ml of zinc hydroxide were not followed by ventricular arrhythmias, although there appeared in the electrocardiogram S-T junction and T wave changes characteristic of the infarct pattern. Multiple injections of zinc hydroxide did result in

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† Vasoxyl, or methoxamine hydrochloride, beta-hydroxy-beta-(2,5-dimethoxyphenyl) isopropylamine, was supplied through the courtesy of Dr. Donald Searle, Burroughs Wellcome & Co., Inc.

premature ventricular systoles, but they were of lesser frequency than those of coronary ligation; they numbered 17 to 28 per cent of the heart beats.

Vasoxyl caused a decrease in frequency or eliminated entirely the ventricular ectopic activity which followed experimental myocardial injury. In animals with the zinc hydroxide-induced arrhythmia, 0.25 mg/kg of Vasoxyl caused complete elimination of ventricular ectopic activity. This same dosage caused only a barely detectable decrease in frequency of ectopic activity in animals with coronary ligation. However, at a dosage of 0.6 mg/kg of Vasoxyl, regular sinus rhythm was restored in all dogs with ligation of the coronary artery. The duration of "antiarrhythmia" protection afforded by Vasoxyl was but 23 to 38 min; the ectopic rhythm eventually returned in all animals.

(2) *Ventricular Arrhythmias Following Overdosage of Cardiac Glycosides in Dogs:* Digoxin (Lanoxin injectable) was slowly administered intravenously to anesthetized dogs during a four-hour time interval; ectopic activity appeared when 0.05 to 0.11 mg/kg had been administered. Because of its short duration of action, acetyl-strophanthidin* was administered by continuous intravenous drip. Arrhythmias followed a dose of 0.09 to 0.36 mg/kg when the acetyl-strophanthidin was given over a 100 minute period. Due to the different duration of action, no quantitative comparison between digitoxin and acetyl-strophanthidin arrhythmia action was possible.

Digitalis-induced arrhythmias varied widely in the ten dogs studied. The appearance of these arrhythmias was heralded by a respiratory sinus arrhythmia, occasionally accompanied by a wandering pacemaker. With larger doses of the cardiac glycosides, sinus tachycardia with variable block or complete atrioventricular dissociation was observed. For the studies in which Vasoxyl was to be used, cardiac glycoside dosage was increased until ventricular arrhythmias appeared; if none appeared, the dog was discarded. The usual form of digitalis-induced ventricular arrhythmia consisted of premature ventricular systoles occurring in bursts of two or three which constituted 13 to 50 per cent of the total heart beats. Bigeminy was next most common; trigeminy and ventricular tachycardia were also observed.

Vasoxyl, in doses of 0.5 to 1.0 mg/kg, eliminated the ventricular arrhythmias induced by digitalis overdosage. Illustrated in Figure 1 is a regular ventricular tachycardia from alternating foci resulting from acetyl-strophanthidin. Despite continuing injection of the acetyl-strophanthidin, Vasoxyl immediately altered the rhythm to one characterized by frequent premature ventricular systoles arising from multiple foci (not shown in Fig. 1). Within 4 minutes after injection of Vasoxyl, a 3:1 or 2:1 atrioventricular rhythm appeared which then changed to regular sinus rhythm with first degree block (P-R interval 0.16 to 0.20 sec). Other arrhythmias resulting from digitalis glycosides (premature ventricular systoles, bigeminy or trigeminy), responded in a similar manner. Following single doses of Vasoxyl, conversion to sinus rhythm was temporary, lasting 20 to 30 minutes.

Procaine amide (Pronestyl) 20 mg/kg also reversed the ventricular arrhythmias from an overdosage of cardiac glycosides, but it appeared that the procaine amide also caused an increase in digitalis heart block. Potassium chloride administered by slow drip also reversed these arrhythmias.

(3) *Amodiaquin-Induced Bigeminal Rhythm:* No suitable procedure exists for the consistent production of bigeminal rhythms in experimental animals. In a brief note[12] it was reported that amodiaquin, an antimalarial drug, resulted in pulsus bigeminus. Thus, amodiaquin† was investigated as a possible means for producing bigeminal rhythm in dogs as an experimental procedure in which antiarrhythmia drugs might be studied.

Dogs (16) were anesthetized with sodium pentobarbital and amodiaquin administered by continuous intravenous infusion. When the rate of

* The acetyl-strophanthidin was obtained through the courtesy of Dr. K. Chen, The Lilly Laboratories, Indianapolis, Indiana.

† Amodiaquin (Camoquin) is chemically 4 (7-chloroquinolylamino)4-diethylamino-ortho-cresol. This material used in our studies was kindly supplied by Dr. A. C. Bratton, Jr., Parke-Davis and Co., Detroit, Michigan.

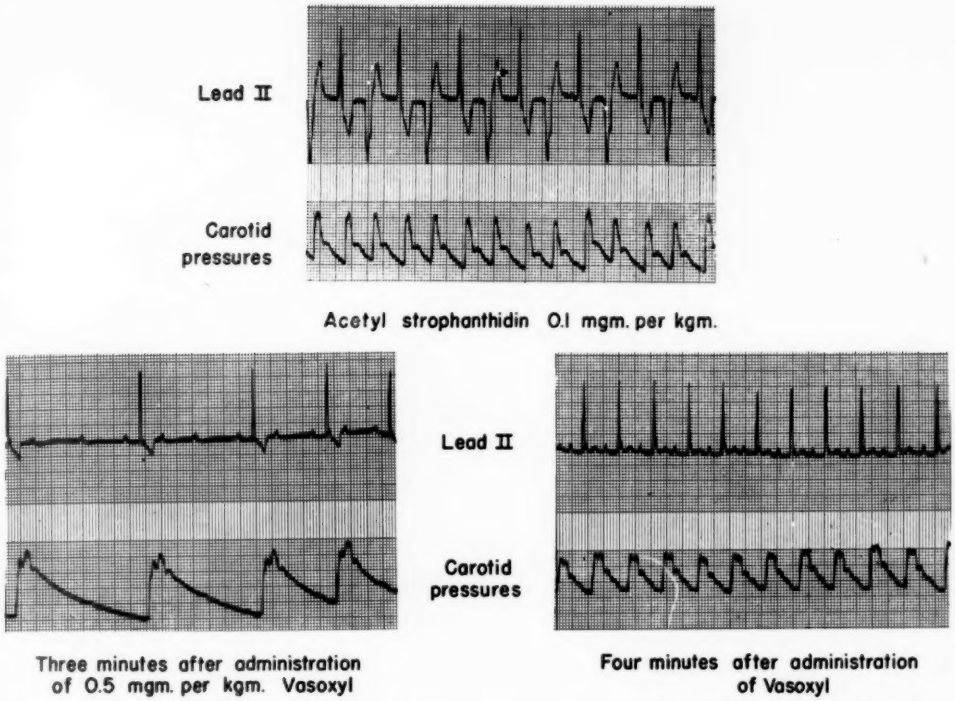

Fig. 1. Conversion by Vasoxyl of ventricular arrhythmia induced in an anesthetized dog by continuous administration of acetyl-strophanthidin. Vasoxyl 0.5 mg/kg was administered over a five-minute period of time. On the lower right, normal sinus rhythm is restored.

injection was 1.0 mg/kg/min, death occurred with a total dose of 35 mg/kg; when the rate was lowered to 0.25 mg/kg/min, lethal dosage increased to 100 mg/kg. Death was due to cardiac failure; there was no significant fall in blood pressure prior to cessation of cardiac activity and respiration was maintained.

Bigeminy appeared when 11 to 50 mg/kg amodiaquin had been administered; the higher dose was associated with the slower rate of infusion. The ectopic beat appears to arise from a fixed focus (the QRS interval was 0.10 sec, compared to the normal of 0.04 sec in the dog). In many examples of the bigeminy, the QRS complexes appeared in opposite directions of simultaneously recorded leads 1 and 3. The coupled rhythm was preceded by a transitory period of premature ventricular contractions arising from varying foci. The terminal arrhythmia which replaced the bigeminal rhythm was a ventricular tachycardia with progressively increasing block and decrease in pulse rate; there was low amplitude of all waves. If the slower rates of injection are selected, amodiaquin's bigeminal rhythm can be maintained for many hours.

When the sustained bigeminal rhythm had been induced by amodiaquin, Vasoxyl at a dose of 0.25 mg/kg failed in each of three dogs to establish sinus rhythm. When, however, the dose was increased to 1.0 mg/kg, the bigeminy was routinely (nine dogs) converted to regular sinus rhythm (Fig. 2). After conversion, the mean heart rate was slightly elevated (108/min) with a measurable prolongation of the P-R interval (0.11 to 0.13 sec). Sinus rhythm persisted for 18 minutes despite continuing perfusion of the amodiaquin.

Vasoxyl Studies in Clinical Ventricular Arrhythmias

Fourteen hospitalized patients were studied. A routine 12-lead electrocardiogram was recorded for each patient, and a continuous record was obtained throughout the administration of Vasoxyl and periodically thereafter. Blood pressures were obtained with a sphygmomanometer at frequent intervals. Vasoxyl was ad-

ministered intravenously by diluting the contents of an ampul, 20 mg, in 250 ml of 5 per cent dextrose. In a few instances the Vasoxyl was given intramuscularly.

(1) *Vasoxyl Administered to Patients with Ventricular Arrhythmias Associated with Myocardial Infarcts:* Vasoxyl was administered first to patients with recent myocardial infarction and hypotension. The initial systolic blood pressures were from 60 to 70 mm Hg, despite efforts to elevate the pressure by the administration of plasma or blood. After intravenous administration of 10 mg of Vasoxyl, the systolic pressures rose to 110 to 130 mm Hg. During this period of time there was a marked reduction or complete disappearance of the premature ventricular systoles. As an example, in one patient

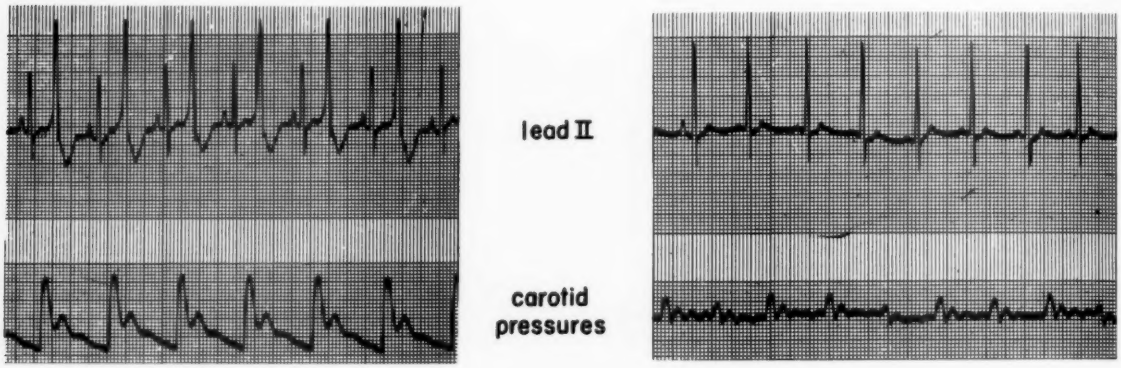

Fig. 2. Bigeminal rhythm in an anesthetized dog resulting from a continuous infusion of amodiaquin. Vasoxyl restores sinus rhythm despite continuing administration of the amodiaquin.

ectopic beats which before therapy occupied 71 per cent of the total heart beats, were reduced at the peak of Vasoxyl action to but 7.4 per cent of the total. It is our impression from the results in the seven cases of myocardial infarction with hypotension, that the greater the frequency of the premature ventricular systoles, the larger the dose of Vasoxyl needed to suppress the ectopic activity. The maximum dose given was 20 mg administered over a 20 minute period of time.

Similar "antiarrhythmic" effects were observed in patients with myocardial infarcts or myocardial insufficiency who were normotensive. Initial systolic pressures ranging from 138 to 150 were elevated to 170 mm Hg by Vasoxyl, and, at the same time, premature ventricular systoles disappeared. When administration of the drug ceased, sinus rhythm persisted for 20–60 minutes; ectopic activity then returned and slowly reached the magnitude it had prior to administration of the drug. Figure 3 illustrates the suppression of a bigeminal rhythm by Vasoxyl administered intramuscularly, with return of ectopic rhythm after the drug had worn off. In 2 patients, the administration of Vasoxyl was resumed and suppression of ectopic activity again obtained.

(2) *Vasoxyl in Digitalis-Intoxication Ventricular Arrhythmias:* Vasoxyl also was found to suppress ventricular arrhythmia believed the result of digitalis intoxication. Since the etiology of the patient's cardiopathy and initial period of decompensation is not entirely clear, this experimental trial of Vasoxyl is presented as a case report. It is our impression that the primary underlying disease is diffuse coronary sclerosis and that excessive digitalization precipitated the acute episode of failure.

Case History

G. C., age 68, entered the hospital in severe congestive failure. There was marked dyspnea and passive congestion of both lungs despite heavy initial digitalization followed by a maintenance dose of 0.25 mg Lanoxin daily for the past three months.

The hospital management consisted of a Karell diet, diuretics, the removal of 1,000 ml of fluid from the right

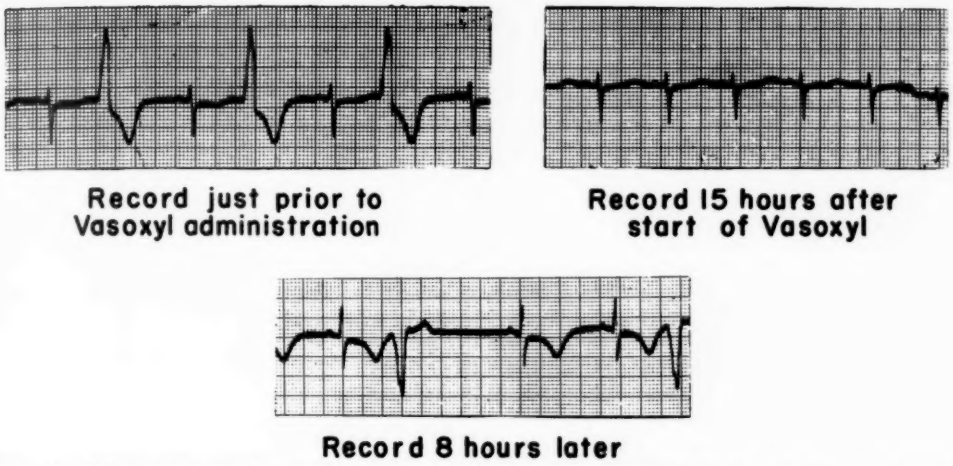

Fig. 3. Effect of Vasoxyl on premature beats in a 70-year-old woman with atherosclerotic heart disease and "old" posterior wall coronary occlusion. The frequent premature ventricular systoles continued despite sedatives and small doses of quinidine. Note the return of sinus rhythm following Vasoxyl administered intramuscularly, in three 20 mg doses at six-hour intervals (lead V_3 in all tracings).

pleural cavity, and the discontinuance of cardiac glycoside therapy because of the presence of multiple ventricular premature beats. In an attempt to increase the potassium levels in the body, 1,000 ml of orange juice per day were added to the Karell diet. The ventricular premature beats, which had been very numerous, gradually decreased in frequency so that on the third hospital day only an occasional premature beat per minute would appear.

On the fourth hospital day the patient was redigitalized; a total of 0.8 mg of acetyl-digitoxin (Acylanid) was administered by mouth in a single dose. Within a few hours a bigeminal rhythm appeared (Fig. 4) and persisted; the blood pressure was 134/82. Despite the bigeminal rhythm, the patient appeared well compensated. Vasoxyl (20 mg in 250 ml of 5 per cent dextrose) was started by intravenous drip and when the drip rate was 60 drops/min, the bigeminy disappeared, to be replaced by a normal sinus rhythm (Fig. 4). The total dose of Vasoxyl given was 10 mg. A few hours later the bigeminal rhythm was again apparent and Vasoxyl was resumed. At this time the drip rate of 120 drops/min again suppressed all ventricular ectopic activity.

The patient was placed on routine therapy for congestive failure (low-salt diet, diuretics, etc.), but digitalis was withheld. When seen three weeks later, the patient was in good compensation. A 12-lead electrocardiogram showed regular sinus rhythm; no ventricular premature beats were present.

(3) *Vasoxyl Administered to Patients with Ven-*

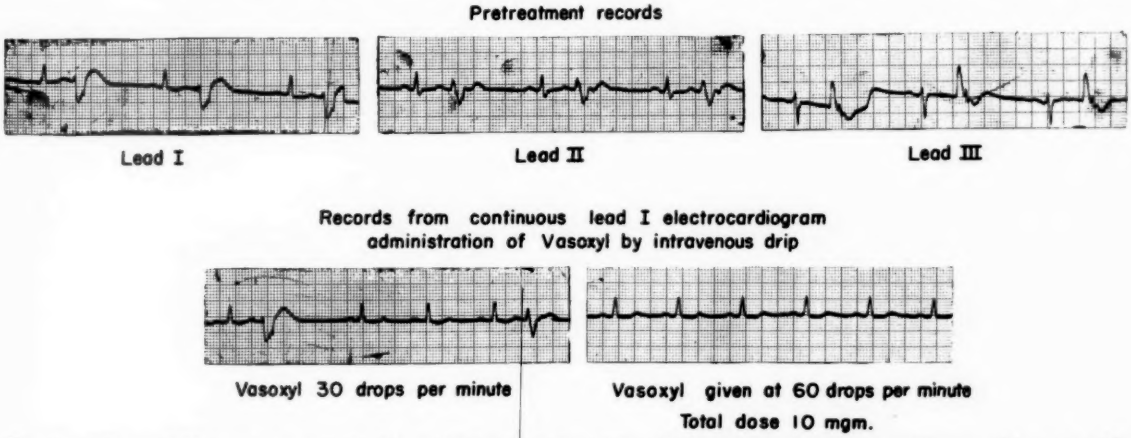

Fig. 4. Effect of Vasoxyl on ventricular arrhythmia induced by digitalis intoxication in a 68-year-old man with severe congestive heart failure. The bigeminal rhythm appeared following 0.8 mg acetyl-digitoxin given by mouth. The lower electrocardiographic records indicate that Vasoxyl with low dosage decreases the frequency of ectopic beats; a larger dose, 10 mg, restores sinus rhythm.

tricular Arrhythmias of Unknown Etiology: Ventricular arrhythmias, either irregular or coupled, occur without any apparent cause. Two such patients are presented. Neither patient had clinical signs or electrocardiographic findings consistent with myocardial insufficiency or infarction. Since these patients were not in apparent congestive heart failure, they were not receiving digitalis. In one patient, a ventricular arrhythmia of multifocal origin appeared after a week's therapy with adrenocorticotropic hormone. The second patient developed a persistent quadrigeminal rhythm while in the hospital under observation for pulmonary emphysema. In both patients Vasoxyl terminated the ventricular arrhythmia for approximately one hour. The multifocal ventricular arrhythmia converted to regular sinus rhythm after but 5 mg of Vasoxyl had been given; the quadrigeminy required 25 mg.

Discussion

Shortly after the introduction of Vasoxyl as a pressor agent, slowing of the normal sinus rhythm was reported as one of its effects. The hypothesis is generally accepted that such bradycrotic action is the result of stimulation of receptors in the aortic arch and carotid sinus, and a reflex discharge of the vagus nerve. Since action of most sympathomimetic amines results rather in a tachycardia, it must also be assumed that they, in addition, possess a positive chronotropic action which dominates the vagal reflex-induced bradycardic effect. The reflex vagal stimulation property of Vasoxyl has been used successfully in the conversion of supraventricular tachycardias to sinus rhythm.[13,14] Since the ventricles are not innervated by the vagus nerve, such a mechanism cannot be accepted for the "antiarrhythmic" action of Vasoxyl for ventricular arrhythmias. Corday[1] suggests that an increase in intracavity pressures and, in turn, increased coronary flow, eliminates the influence of a ventricular ectopic focus. Gilbert, Lange, and Brooks[15] report that, on the heart, Vasoxyl prolongs the action potential, prolongs the absolute refractory period, raises the threshold to stimulation and slows A-V conduction. This would suggest that Vasoxyl may exert an antifibrillatory action independent of its pressor effect. In our clinical experiments, Vasoxyl appeared to be equally effective in patients whose initial pressures were at shock levels, as well as in those whose pressures were within normal limits.

It is apparent that in view of the small number of patients involved, our observations with Vasoxyl as an antiarrhythmic drug must be considered preliminary. The short time period of effectiveness is a handicap for Vasoxyl's use as a therapeutic agent. However, discovery of an antiarrhythmic quality in a class of drugs, pressor amines, generally considered only to provoke arrhythmias is important. Modification of Vasoxyl's structure may produce a new derivative with practical merit in therapy of ventricular arrhythmias.

Summary

Ventricular arrhythmias were established in dogs by ligation of the anterior descending coronary artery; by the production of myocardial necrosis with the injection of zinc hydroxide; by the administration of toxic doses of various cardiac glycosides; and by a new experimental procedure consisting of infusing amodiaquin solution until a bigeminal rhythm has been produced. In animals with these various ventricular arrhythmias, Vasoxyl hydrochloride administered in dosages of 0.5 to 1 mg/kg of body weight was found capable of suppressing the arrhythmias for periods of 30 to 60 minutes.

The antiarrhythmic property of Vasoxyl was confirmed in patients. Used in similar dosages, Vasoxyl was able to suppress significantly or eliminate completely various ventricular arrhythmias ranging from the occasional premature ventricular systoles to multifocal ventricular tachycardias. Included in the therapeutic range of Vasoxyl are arrhythmias associated with myocardial infarction, digitalis intoxication, and heart disease of idiopathic origin. As in the experimental animal, Vasoxyl in single doses was capable of suppressing clinical ventricular arrhythmias in most instances for periods of 20 to 40 minutes.

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The Bradycrotic Action of Reserpine in Atrial Fibrillation with Rapid Ventricular Rates

Results in 16 Cases with Organic Heart Disease*

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THE bradycrotic and hypotensive action of reserpine on the cardiovascular system as well as its more widely publicized tranquilizing and sedative effect on the central nervous system are well known. Less familiar, however, is the effect of reserpine on the ectopic arrhythmias, and the paucity of information available in this condition prompted the present investigation. Atrial fibrillation was chosen principally because of its frequency, its permanency, and the relative ease with which it could be graphically recorded. It is one of the two commonest forms of disordered heart action, being surpassed in frequency only by premature systoles. Atrial fibrillation may be found in either a paroxysmal or permanent form but usually occurs with greater frequency in the latter group. Paroxysmal atrial fibrillation may be present in acute myocardial infarction, pneumonia, operative chest procedures, etc., but is particularly characteristic of hyperthyroidism. It is obvious, therefore, that the paroxysmal variety of atrial fibrillation often occurs in individuals with apparently normal hearts. The permanent form of atrial fibrillation, on the other hand, is most often associated with overt heart disease and congestive failure.

Rheumatic heart disease with mitral stenosis, coronary arteriosclerotic heart disease, and hypertension represent the most frequent organic cardiac lesions coexistent with this arrhythmia in its permanent form.

No age or sex is exempt from atrial fibrillation. In coronary artery disease, males in the older age groups predominate. Conversely, in hyperthyroidism and mitral stenosis, there is a greater incidence among the younger females.

The ventricular response to the rapid and irregular auricular activity is the sine qua non which will be the determining factor as to whether congestive heart failure is precipitated or not. Consequently, the aim of therapy is to achieve a sufficiently slow ventricular rate to permit adequate diastolic filling of the ventricle and an enhanced coronary blood flow.

The purpose of this paper is to report the effect of reserpine† in 16 patients with chronic organic cardiovascular disease who had atrial fibrillation in association with a rapid ventricular rate. Six representative case narratives with electrocardiographic features follow.

CASE HISTORIES

CASE 1. G. H., a 53-year-old white male, was admitted to the hospital for the fourth time because of shortness of breath, right chest pain, and cough of six months' duration. His first hospitalization, due to an abscessed tooth, occurred in 1938 during which an enlarged

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† The reserpine used in this study was supplied as Serpasil through the courtesy of Ciba Pharmaceutical Products Inc.

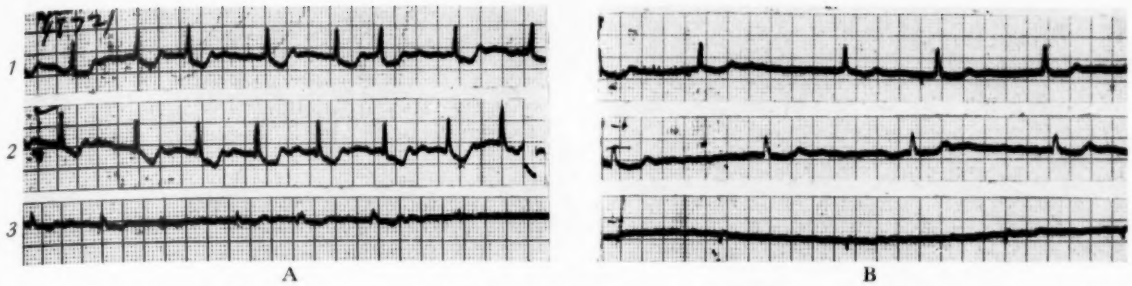

Fig. 1. Case 1. (A) Initial electrocardiogram on admission. Atrial fibrillation with a ventricular rate of 100. Digitalis T wave effects present. (B) Electrocardiogram six days after reserpine administration. Atrial fibrillation with a ventricular rate of 55. Digitalis effects are no longer evident.

heart and atrial fibrillation were discovered. He admitted having migratory joint pains in 1932 at the age of 29 years. In 1949, he was hospitalized for the second time, the chief complaints being shortness of breath and swelling of his extremities for the previous year. Examination at that time revealed cardiac enlargement extending to the anterior axillary line, a right pleural effusion, and atrial fibrillation. His electrocardiogram confirmed the presence of atrial fibrillation with a ventricular rate of 75/min and no axis deviation. He was placed on 0.1 mg digitaline nativelle daily. Four years later, in 1953, he sought admission to the hospital for the third time because of cough, shortness of breath, abdominal swelling, and edema of the extremities. A chest roentgenogram demonstrated the presence of congestive changes in both lung fields.

His fourth admission, presently being reported, took place on November 6, 1956 for the identical complaints which marked his three previous hospitalizations. A chest film showed a resolving effusion at the base of the right lung. The heart was found to be clinically enlarged. The point of maximum intensity was in the 5th intercostal space in the anterior axillary line, and a systolic thrill was felt at the apex. There was a snapping 1st sound at the apical area followed by a low-pitched diastolic rumble. The blood pressure was 140/90. No peripheral edema was noted. The venous pressure was 62 mm of water. The arm-to-tongue time (Decholin) was 30 sec and the arm-to-lung time (ether) was 9 sec. The electrocardiographic tracing showed atrial fibrillation with a rapid ventricular rate and a left deviation of the electrical axis. His cardiac diagnosis was rheumatic cardiovascular disease (inactive) with an enlarged heart, mitral insufficiency and stenosis, atrial fibrillation, and left ventricular failure with a right hydrothorax.

Effects of Reserpine Therapy: The patient had been taking 0.5 mg. digoxin once daily prior to entry into the hospital and this therapy was promptly suspended. Upon admission he was given reserpine 0.25 mg three times daily for four days. Thereafter, he was maintained on a daily dose of 0.25 mg. The initial electrocardiogram on admission showed atrial fibrillation with a ventricular rate of 100/min and digitalis effects (ST depressions and T wave inversions) (Fig. 1A). Six days later on reserpine therapy alone, the atrial fibrillation was still evident but the ventricular rate had been slowed to 55 per min (Fig. 1B). The digitalis effects seen on the original electrocardiogram were no longer present in the reserpinized tracing. The blood pressure was lowered to 126/80. The slowing of the ventricular rate with reserpine persisted for the next six weeks until December 24, 1956 when he was discharged from the hospital. The patient's signs and symptoms of congestive failure improved perceptibly with the slowing of the ventricular rate by reserpine.

During this patient's hospital stay, it was decided to administer atropine sulfate to determine whether the action of reserpine was mediated through the vagus nerve or whether there was a direct myocardial effect or both. One milligram of atropine sulfate was injected subcutaneously. Thirty minutes later his ventricular rate rose from a control of 69/min to 82/min. The ventricular rate returned to its original level after the atropine effect had disappeared.

One week after discharge, the patient was readmitted to the hospital for the fifth time because of shortness of breath, progressive leg edema and cyanosis of 36 hours' duration. He stated that he had neglected to continue taking his reserpine. Before any corrective measures could be taken to control his congestive failure, the patient signed himself out of the hospital the day following his last admission.

COMMENT

This case illustrated the successful employment of the reserpine alkaloid in slowing the ventricular rate in atrial fibrillation from a peak rate of 100/min to 55/min within a six-day period. The reserpine alkaloid was effectively substituted for the digitalis glycoside. It would appear that reserpine has a bradycrotic central vagotonic action, since atropine administration resulted in an increase in ventricular rate which disappeared when the atropine effect wore off. The hypotensive value of reserpine was apparent in this case. The failure of this patient to continue his maintenance dose of reserpine re-

sulted in a recurrence of his rapid atrial fibrillation and a return of his congestive symptomatology.

CASE 2. W. P., a 79-year-old white male, entered the hospital on November 28, 1956, because of dyspnea, edema, and 4+ glycosuria. The essential findings on admission were an enlarged heart, atrial fibrillation with a ventricular rate of 150/min. The blood pressure was 155/70. He had both right and left congestive failure with rales at both lung bases, a 3-finger palpable liver, and 4+ pitting edema. The blood sugar was 298 mg and the urine showed 4+ glycosuria. His venous pressure was 200 mm of water. The Decholin arm-to-tongue time was 33 sec and the ether arm-to-lung time was 16 sec. An electrocardiogram taken on the day following admission showed atrial fibrillation with a ventricular rate of 110/min, low voltage and left axis deviation (Fig. 2A). A chest film revealed an enlarged heart in all diameters with a widening of the supracardiac portion of the aorta. The lungs exhibited bilateral congestive changes.

The diagnosis was arteriosclerotic cardiovascular disease with an enlarged heart, atrial fibrillation with a rapid ventricular rate, congestive heart failure and diabetes mellitus. He was given reserpine 3 mg daily for three days, following which he was maintained on 0.5 mg daily. Seven days after initiating reserpine therapy, the ventricular rate was slowed to 64/min and the blood pressure declined to 130/60. The bradycrotic response to reserpine was seen in the electrocardiogram taken on December 9, 1956 (Fig. 2B). However, the atrial fibrillation persisted but with a considerably slower ventricular rate, ranging between 65 and 72/min. All the signs and symptoms of an overtaxed myocardium subsided spontaneously and, with the control of his diabetic status, he was discharged from the hospital to the Home Care Service, thirty-nine days after admission.

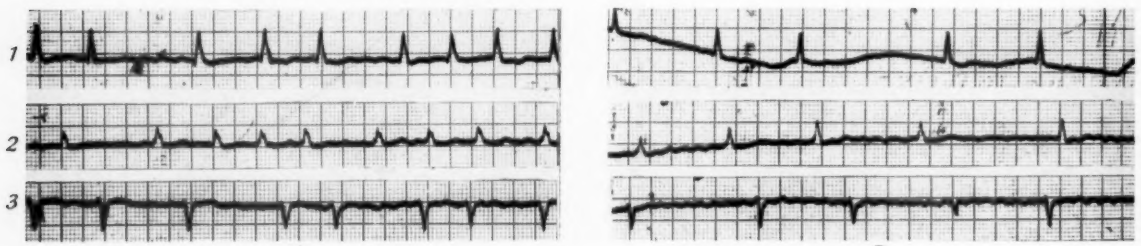

Fig. 2. Case 2. (A) Initial electrocardiogram on admission. Atrial fibrillation with a ventricular rate of 110. Left axis deviation. (B) Electrocardiogram taken seven days after instituting reserpine therapy. Atrial fibrillation with a ventricular rate of 64.

COMMENT

This patient clearly demonstrated the bradycrotic effectiveness of reserpine in controlling the rapid ventricular rate in atrial fibrillation. Worthy of mention was the spontaneous disappearance of the congestive failure subsequent to adequate regulation of the ventricular rate with reserpine. Finally, it should be noted that overt slowing of the ventricular rate in this case required seven days.

CASE 3. W. D., a 79-year-old white male, was first seen on December 13, 1956, complaining of dyspnea, orthopnea, cough, and edema of the legs which had become progressively more severe during the previous four months. He stated that the shortness of breath had been present for three years. He denied having had hypertension, diabetes mellitus, rheumatic fever, syphilis, kidney infection, or pulmonary tuberculosis.

Physical examination revealed a confused and disoriented patient with overt dyspnea, orthopnea and pulsating cervical veins but no cyanosis. The heart was enlarged with the apical impulse well outside the midclavicular line. No thrills or murmurs were found. The rhythm was totally irregular with a ventricular rate of 96/min. The blood pressure was 110/80. The lungs revealed dullness and decreased voice sounds at the right base. Numerous moist rales were audible over both lung fields. The liver was palpated three fingerbreadths below the costal margin and there was 3+ peripheral edema. The electrocardiogram taken shortly after admission showed atrial fibrillation with multiple ventricular premature systoles (Fig. 3A). The precordial leads V_{4-6} exhibited changes consistent with an old anterolateral myocardial infarction. The clinical diagnosis was arteriosclerotic cardiovascular disease with an old anterolateral myocardial infarction, atrial fibrillation, frequent ventricular extrasystoles, and congestive failure with a right hydrothorax.

The patient was started on a regimen of complete bed rest, 0.5 g theophylline intravenously, a restricted sodium intake and oxygen for five days in order to stabilize the patient's condition. Reserpine was administered on December 18, 1956. A second electrocardiogram was taken on December 24, the sixth day after instituting reserpine therapy (Fig. 3B). It revealed the complete abolition of the numerous ventricular extrasystoles which were observed in his previous tracing. The initial dosage

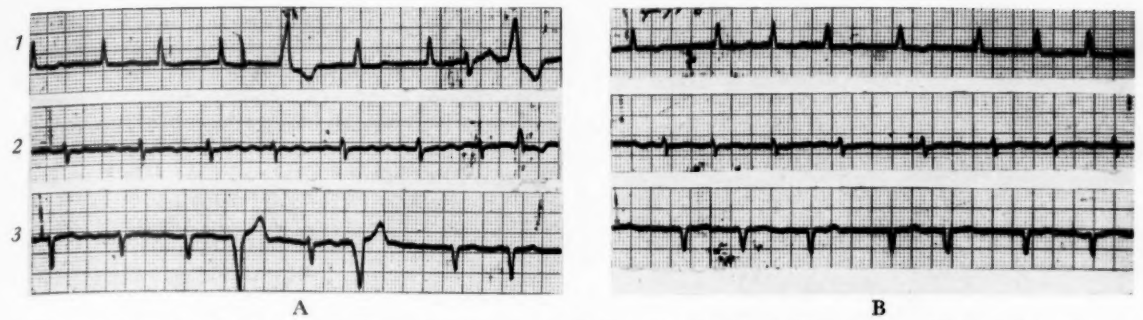

Fig. 3. Case 3. (A) Initial electrocardiogram on admission. Atrial fibrillation with multiple ventricular premature systoles. Ventricular rate of 90. Left axis deviation. (B) Electrocardiogram after six days of reserpine therapy. Atrial fibrillation still present but the ventricular extrasystoles have disappeared.

of reserpine used was 0.25 mg three times daily for four days. This was then decreased to a maintenance dose of 0.25 mg once daily. He did well for the next three weeks with considerable improvement of his congestive failure when he developed a cerebral embolus and expired suddenly.

COMMENT

The promising result which reserpine displayed in abolishing the many ventricular extrasystoles was well exemplified in this patient. However, it required six days for the reserpine alkaloid to accomplish this result. The ventricular rate, though not particularly rapid, was slowed from 90 to 80 beats/min. Death was attributable to one of the major vascular catastrophes so common in atrial fibrillation, namely, the loosening of a small fragment from a mural thrombus adherent to the left auricular wall and its subsequent lodgment in some vital structure of the body. Postmortem examination confirmed the clinical findings in this man.

CASE 4. D. F. was an 83-year-old Negro male, who sought hospitalization on November 28, 1957, because of persistent diarrhea, fever, and profuse perspiration of two weeks' duration and shortness of breath for the previous 12 years but becoming progressively worse in the 10 months prior to admission. He noted some precordial discomfort on slight exertion but emphatically denied any definite chest pain. He did admit some palpitation, however, and an occasional cough, worse at night, for the past four years. He never had hypertension, rheumatic fever, syphilis, diabetes mellitus, or pulmonary tuberculosis.

The admission physical findings revealed a restless elderly Negro male, dyspneic, orthopneic, coughing spasmodically, drowsy and, at times, rambling and incoherent, looking both acutely and chronically ill. The cervical veins were moderately distended but did not fill from below. The heart was enlarged with the apical thrust in the anterior axillary line. No murmurs were audible. There was a rapid, completely irregular rhythm with a ventricular rate of 120/min and pulse rate 105, leaving an appreciable pulse deficit of 15 beats. The blood pressure was 128/80. Bilateral pulmonary basal rales were heard; the liver edge was palpated three fingerbreadths below the costal margin but no peripheral pitting edema was observed.

The admission electrocardiogram disclosed atrial fibrillation with a ventricular rate of 120/min and right bundle branch block (Fig. 4A). The roentgenogram revealed a cardiac silhouette enlarged in all diameters, marked widening of the supracardiac aorta, and congestion in both lung fields. The clinical impression was

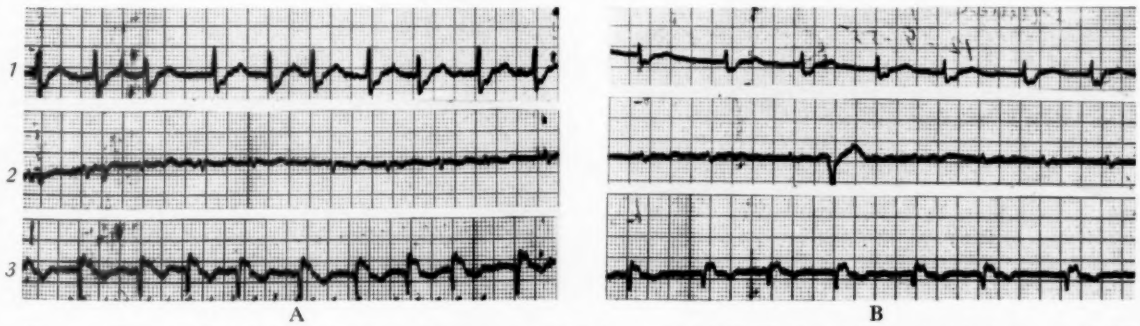

Fig. 4. Case 4. (A) Initial electrocardiogram on admission. Atrial fibrillation with a ventricular rate of 120. Right bundle branch block. (B) Electrocardiogram taken six days after reserpine administration. Atrial fibrillation with a ventricular rate of 80–90.

arteriosclerotic cardiovascular disease with an enlarged heart and widened aorta, atrial fibrillation with a rapid ventricular rate, right bundle branch block and left ventricular failure.

He was placed on a control regimen of absolute bed rest, oxygen by mask, barbiturates and theophylline 0.5 g intravenously for the next five days. Reserpine therapy was then instituted on December 4, 1957, starting with 1 mg of the alkaloid daily for four consecutive days and followed by a maintenance dose of 0.5 mg daily. Six days following initial reserpinization, the ventricular rate dropped to 84/min, the pulse rate to 80, and the blood pressure to 100/64. The ventricular slowing was exemplified in the second electrocardiographic strip taken on December 12, 1957 (Fig. 4B). Three subsequent electrocardiograms taken during the remainder of his hospital course continued to graphically demonstrate the slow ventricular rate. The bilateral chest rales cleared and dyspnea was immeasurably improved. However, on the 17th day of reserpine therapy, the patient exhibited unruly and boisterous outbursts on the ward. This abnormal behavior pattern subsided when the dosage was cut to 0.25 mg daily. He was maintained on this schedule for his final three weeks in the hospital. On January 9, 1958, he was discharged from the hospital considerably improved, with a ventricular rate of 70, no pulse deficit, a blood pressure of 105/80, and without any evidences of congestive failure.

COMMENT

This case was of interest in demonstrating once again the ability of reserpine in maintaining a well-controlled ventricular rate in atrial fibrillation. Moreover, it emphasized the necessity of constantly being alert for the appearance of drug reactions, which in this case was manifested by a bizarre psychiatric behavior. The immediate reduction of the reserpine dosage sufficed to produce a calm and cooperative patient, while the beneficial cardiovascular effects persisted unchanged.

CASE 5. F. H. was a 67-year-old white male who entered the hospital on December 16, 1956, with a one-month history of progressive shortness of breath and swelling of both legs of one week's duration. There was no evidence of rheumatic infection, syphilis, hypertension or tuberculosis either from the history or physical examination.

The patient was an obese, elderly white male who was dyspneic and orthopneic and looking acutely ill. The relevant physical findings were limited to the cardiovascular system. The neck veins were dilated and pulsatile. The heart was clinically enlarged with the point of maximum intensity in the 6th intercostal space, well outside the midclavicular line. There was a loud blowing systolic apical murmur transmitted upward toward the aortic area. The rhythm was totally irregular with a ventricular rate of 150/min. The blood pressure was 120/80. There was 3+ peripheral edema. A chest roentgenogram showed a heart markedly enlarged in all diameters, with straightening of the left cardiac border. There were congestive changes in both lung fields. A control electrocardiogram was obtained the day following admission and was interpreted as showing atrial fibrillation with a rapid ventricular rate of 150 but without any axis deviation (Fig. 5A). A diagnosis of arteriosclerotic cardiovascular disease was made, with atrial fibrillation and rapid ventricular rate and congestive heart failure.

He was placed on a regimen of complete bed rest, theophylline, Mercuhydrin, and general supportive therapy, for a three-day stabilization period. Reserpine was then begun with 0.75 mg daily for four days followed by a maintenance dose of 0.25 mg/day. On the fifth day of reserpine administration the ventricular rate was substantially decreased to between 80 and 90/min (Fig. 5B). This bradycrotic effect persisted until his transfer to another hospital three months later. It might be added parenthetically that the signs and symptoms of congestive failure subsided simultaneously with the slower ventricular rate.

COMMENT

This patient showed a good bradycrotic re-

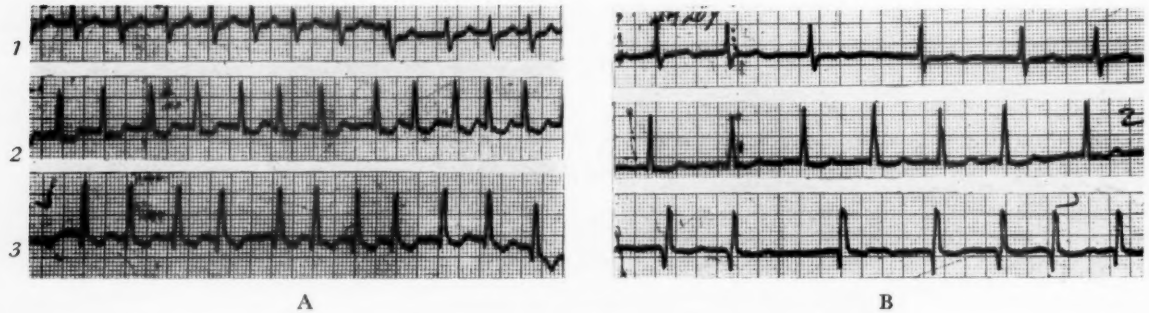

Fig. 5. Case 5. (A) Initial electrocardiogram on admission. Atrial fibrillation with a ventricular rate of 150. (B) Electrocardiogram five days after reserpine administration. Ventricular rate slowed to between 80 and 90. Atrial fibrillation still evident.

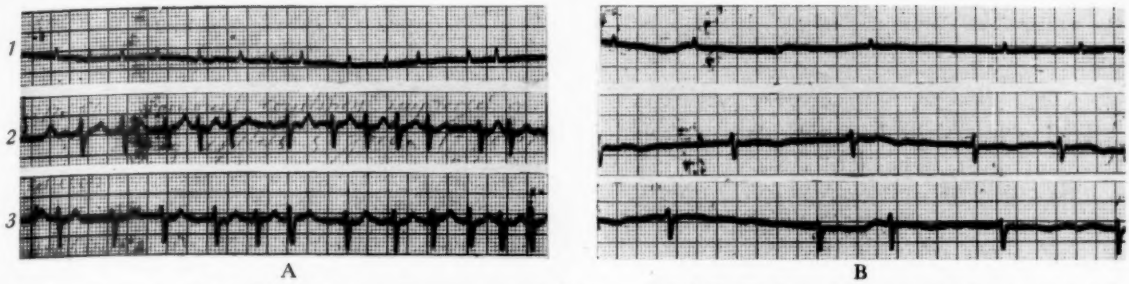

Fig. 6. Case 6. (A) Initial electrocardiogram on admission. Atrial fibrillation with a ventricular rate of 140. Left axis deviation. (B) Electrocardiogram four days after reserpine instituted. Atrial fibrillation with a ventricular rate of 55.

sponse to reserpine therapy. His ventricular rate was slowed from 150 to 90/min on the fifth postreserpine day. A follow-up of this patient in another hospital one year later was interesting from two viewpoints. First, the ventricular control was maintained for an additional six months with reserpine, thus totaling an over-all combined average of nine consecutive months in both hospitals. Subsequently, the digitalis glycosides were substituted for the reserpine alkaloid. Finally, the patient developed arteriosclerotic peripheral vascular disease with intermittent claudication during his present hospitalization. This was considered further evidence of the inexorable progress of his arteriosclerotic lesions, from obvious cardiac involvement to a disabling peripheral obliterative process.

CASE 6. J. O. was a 68-year-old white male who was hospitalized on November 2, 1956, because of a four-week history of shortness of breath, cough, and chest pain. At first the dyspnea developed after moderate effort but gradually became progressively worse with little or no exertion. A productive cough which had been present for many years became worse prior to his hospital entry and was associated with bilateral chest pain. Deep inspiration and coughing aggravated the chest discomfort. There was no hemoptysis or night sweats. One week before admission swelling of the legs was noted by the patient. There was no history of hypertension, rheumatic polyarthritis, syphilis, diabetes mellitus, or tuberculosis. He did admit that he was a casualty of mustard gas poisoning in World War I.

The patient was thin and of poor nutritional status, dyspneic but not cyanotic, well-oriented and looking acutely ill. The significant physical findings were dilated neck veins, pulsating irregularly. The heart was not clinically enlarged nor were there any audible murmurs or palpable thrills. The rhythm was totally irregular with a ventricular rate of 120 and a pulse rate of 100/min. The blood pressure was 120/65. The chest was emphysematous in type and there were basal rales with diffuse inspiratory and expiratory wheezes scattered over the lung fields. The liver and spleen were not palpable. There was 2+ pitting edema over both lower extremities. A marked degree of hypertrophic pulmonary osteoarthropathy involving the distal phalanges of the fingers and toes was noted. The electrocardiogram taken on the day after admission showed atrial fibrillation with a rapid ventricular rate of 140/min and left axis deviation (Fig. 6A). A roentgenogram revealed a normal cardiac configuration and irregular bronchiectatic changes in the lower half of the right lung. The clinical impression was arteriosclerotic cardiovascular disease, atrial fibrillation with a rapid ventricular rate, congestive failure, chronic bronchopulmonary disease with bronchiectasis and emphysema.

The initial therapy consisted of a three-day preliminary control period of complete bed rest, oxygen, theophylline, and general supportive measures. This was followed by a reserpine loading dose of 0.75 mg daily for four days, which was then reduced to a maintenance level of 0.25 mg daily thereafter. Four days after commencing the reserpine alkaloid the ventricular rate was slowed to 55–60/min and this result was graphically portrayed in the second electrocardiogram (Fig. 6B). The hypotensive action of reserpine was similarly demonstrated, namely a systolic pressure of 104 and a diastolic of 50. The patient's course while in the hospital during the succeeding four weeks was uneventful and his ventricular rate was well controlled with 0.25 mg reserpine daily. The congestive heart failure subsided and the patient was considerably improved subjectively with the slower ventricular rate. However, on December 7, a month after his admission, the patient suddenly complained of epigastric pain and weakness. Emesis of large volumes of black, coffee-ground material occurred 15 minutes later. Within 3 hours after the onset of the upper gastrointestinal bleeding, his ventricular rate rose from 70 to 112/min despite the daily administration of the reserpine alkaloid. The drug was suspended immediately. The massive hemorrhage persisted despite all efforts to stem the bleeding. The blood pressure dropped to shock levels of 60–40 systolic and 20–0 diastolic. He expired within 6 hours from severe, uncontrollable alimentary bleeding.

COMMENT

There were several interesting aspects of this case which should be emphasized, although they were not strictly applicable to the cardiovascular system. First, it must be pointed out as heretofore stated that this patient became a pulmonary cripple as a result of mustard gas poisoning in World War I. This caused him to become susceptible to numerous pulmonary infections and the production of irreversible damage to the elastic structure of the bronchial tree. The subsequent development of bronchiectasis of the right lung was a foregone conclusion. Nevertheless, this patient was able to span the adult years and live to become an arteriosclerotic cardiac with atrial fibrillation.

The beneficial bradycrotic and hypotensive value of reserpine was clinically demonstrated in this case. However, one of the serious complications attributable to reserpine therapy occurred, namely, severe and, in this instance, fatal upper gastrointestinal bleeding. Notwithstanding a negative history of a peptic ulcer and absent findings suggestive of a gastric or duodenal lesion, this patient suffered a fatal hemorrhage, nonetheless. Parenthetically, it might be added that a gastrointestinal roentgen series was taken eight months previously at another institution because of his cachectic appearance and the suspicion of a silent neoplasm of the alimentary tract. The x-ray films were entirely negative, however. The problem of how this unfortunate tragedy could have been prevented with the available facts at hand was difficult to resolve.

Finally, there occurred a ventricular escape phenomenon from reserpine control with the appearance of shock due to massive hemorrhage. Within a short span of three hours the ventricular rate rose to 110/minute in response to the clinical picture of hemorrhagic shock. Consequently, an uncontrolled rapid ventricular rate was superimposed upon the shock of exsanguination and the inevitable outcome was complete circulatory collapse and death.

Discussion

Reserpine is a crystalline alkaloid derived from the root of the *Rauwolfia serpentina*, a plant of the dogbane group indigenous to India. Extracts of the roots of *Rauwolfia serpentina* have been employed for centuries in the folklore of ancient Indian medicine. From this morass of fact and fancy have emerged several scientifically proven truths, namely, a tranquilizing or sedative action, a hypotensive effect, and a bradycrotic response. In 1931 the Indian chemists, Siddiqui and Siddiqui,[1] announced the isolation of five different alkaloids from rauwolfia. In 1952, Muller, Schlittler and Bein[2] first isolated the alkaloid reserpine in pure crystalline form. In 1956, Woodward synthesized the white crystal of pure reserpine for the first time.

The introduction and universal acceptance of the reserpine alkaloid for its tranquilizing effect in neuropsychiatric disorders have tended to overshadow its use in cardiovascular diseases. While it has been generally conceded that reserpine has a bradycrotic action on sinus rhythm without reducing the cardiac output or the stroke volume, its therapeutic value has not yet been adequately investigated in ectopic rhythms. As far as we could ascertain, there have been no previous reports in the literature regarding the use of reserpine in slowing the rapid ventricular rates in atrial fibrillation. Our main object, therefore, was to determine whether reserpine could produce a bradycrotic response in the arrhythmia. With this objective in mind, 16 cases of atrial fibrillation with a rapid ventricular rate were selected for critical evaluation. All of these patients were chronic fibrillators with severe, underlying organic heart disease. The paucity of our material ruled against the drawing of any final conclusions, but it was hoped that a definite trend would be discernible as the study progressed.

Clinical Results of Reserpine Therapy: Reserpine proved unquestionably successful as a bradycrotic agent in 12 of the 16 cases of atrial fibrillation in this study. The reason for the four failures in this group was obscure and difficult to explain. One can only speculate on the possibility of a dual etiology in the production of atrial fibrillation, viz., increased vagal tone associated with some toxic or anoxic factor. There is a considerable body of evidence in support of this theory. Nahum and Hoff[3] injected

acetyl-B-methylcholine (Mecholyl) intramuscularly in thyrotoxic patients with a normal sinus rhythm and successfully induced a transitory atrial fibrillation. It has been shown by numerous investigators, Bruenn,[4] Keith,[5] and others, that prolongation of the P-R interval in rheumatic cardiovascular disease is a manifestation of vagal activity in a large percentage of cases. Altschule[6] demonstrated a high degree of correlation between a prolonged P-R interval and the appearance of atrial fibrillation in 55 consecutive rheumatic cardiacs of whom 21 subsequently developed atrial fibrillation. Smith and Wilson[7] investigated the relationship between the induction of atrial fibrillation and anoxemia of the auricles and vagal stimulation (Mecholyl effect) in a series of experiments on dogs' hearts. They showed that anoxemia and auricular distention made the heart more susceptible to the action of Mecholyl and facilitated the production of atrial fibrillation.

Six of our 12 successful cases with atrial fibrillation were chosen as representative examples of the bradycrotic effectiveness of reserpine. The clinical features and electrocardiographic patterns, both before and after reserpine administration, were followed throughout their hospital course. The results in this sample group were identical with the observations in the entire group of twelve under investigation, namely, a slowing of the rapid ventricular rate in atrial fibrillation. Consequently, one can conclude that the modus operandi of the reserpine alkaloid resembles the digitalis glycoside in producing a vagal effect but differs in that reserpine does not elicit a direct myocardial response.[8,9] However, the vagotonic hyperactivity of reserpine is not due to a direct parasympathetic stimulation but is secondary to a proportionate weakening of its sympathetic antagonist. Thus, the increased vagal activity due to reserpine is a relative and not an absolute intangible in the sympathetic-parasympathetic equilibrium. On the other hand, atropine by blocking vagal impulses tends to restore this equilibrium which was disrupted by reserpine. Schneider,[8] from his cat experiments, concluded that reserpine slowed the heart by a central block of the afferent impulses which normally stimulate sympathetic responses and thus confirmed Bein's[10] pharmacological observations reported earlier.

Previous Studies of Reserpine Effect on Heart Rate and Rhythm: The exact mechanism by which reserpine exerts its effect in atrial fibrillation remains obscure. However, there is general agreement regarding the locus of its action, which favors a central site, presumably in the hypothalamus.[22]

Bixby[11] used reserpine in six cases of paroxysmal tachycardia, of which half were improved. He stated that this therapy failed when the paroxysms were a complication of underlying organic heart disease. Furthermore, he found the best results occurred when the arrhythmia was due to neurogenic factors. Finally, he concluded that the reserpine alkaloid was effective only in preventing paroxysmal tachycardia and not in restoring it to a normal sinus rhythm. The possibility of inadequate dosage of reserpine under the circumstances described by Bixby is a very plausible one. He utilized a daily dose ranging between 0.25 mg to 1 mg in his successful cases. No mention is made concerning the dosage schedule of his three failures.

Caputi[12] described the favorable effects of reserpine in two cases of supraventricular and atrial tachycardia utilizing doses of 0.25 mg daily. He failed to detect the presence of organic heart disease in both cases after a careful search.

In a series of 30 ambulatory patients with organic heart disease, tachycardia, and symptoms of emotional tension, Halprin[13] reported symptomatic improvement and the relief of tachycardia using 0.4 mg of reserpine daily. His cases comprised coronary heart disease, neurocirculatory asthenia, thyrotoxicosis and premature contractions. Schumann and Rehberg[14] employed reserpine in 73 cardiac cases using a daily dose of 1.25 mg. Their aim was to evaluate its bradycrotic potential, and they reported a favorable result occurring within 24 to 48 hours after initial reserpine administration.

Cotten *et al.*,[15] in a series of 98 ambulatory hypertensive patients treated with reserpine, were able to demonstrate a significant slowing of the heart rate in approximately half of their cases.

Hollister[16] observed two cases of intermittent bundle branch block in which reserpine reversed the conduction defect. He was unable to ex-

plain the mechanism involved in terminating the block, but in one patient the pathologic findings confirmed the presence of an incomplete lesion of the bundle of His underlying the intermittent bundle branch block. Hollister administered between 2 and 3 mg reserpine daily.

On the other hand, Harris[17] described a patient who developed paroxysmal atrial fibrillation while taking reserpine. Quinidine converted the arrhythmia to sinus rhythm and subsequently the arrhythmia recurred on placebo therapy. He concluded that reserpine was not responsible for the development of this ectopic rhythm.

Latent Period of Reserpine Effect: The characteristic long latent period of reserpine was an obvious disadvantage in this study, particularly where it was necessary to slow the rapid ventricular rate in atrial fibrillation as quickly as possible. The frequent association of congestive failure with this arrhythmia made mandatory its early control. It required from three to seven days to slow the ventricular rate sufficiently to insure an adequate cardiac output. This is in accord with the experience of many investigators with reserpine. It must be remembered that our patients were given the drug by the oral route. The possibility of curtailing the latent period by the parenteral administration of the rauwolfia alkaloid offers a fruitful field for future investigation.

Combined Reserpine and Digitalis Therapy: Another alternate solution to the problem of reserpine lag is the concomitant use of digitalis with reserpine. The numerous advantages of such combined therapy are obvious. Thus, smaller doses of both drugs can be given, lessening the hazard of digitalis toxicity. This was borne out by the investigations of Klausgraber,[18] and Mattoli and Atlante.[19] Furthermore, the urgency to control the ventricular rate with the slower acting reserpine would be diminished appreciably because of the more rapid digitalis action. Finally, the salutary effect of reserpine in sedating and tranquilizing the emotional stresses of these patients cannot be ignored.

Fluid Retention During Reserpine Therapy: In 10 of the 16 patients we were able to weigh, no evidence of fluid accumulation was found. The remaining 6 patients were bedridden and too ill to be moved. Perera[20] observed fluid retention in five hypertensive patients treated with rauwolfia preparations. In two of his five patients, the degree of fluid retention was so severe that it precipitated congestive heart failure. However, water retention is considered a rather uncommon sequela of rauwolfia therapy.

Reserpine Dosage: The dosage of reserpine was larger during the early exploratory phase of this investigation than that employed later in this group. The first few cases received 1 mg of reserpine three times daily for 3 or 4 days. The maintenance level was then adjusted to 0.5 mg in divided doses daily thereafter. Later in the course of this investigation, it was felt that initial reserpinization with 3 mg daily was excessive. Consequently, the loading dose was reduced to 0.75–1 mg daily for three days, followed by a maintenance dose of 0.25–0.5 mg daily. This latter more conventional dosage schedule proved to be therapeutically satisfactory since maximum effectiveness was achieved in controlling the ventricular rate for the balance of the study.

Side Effects of Reserpine: Sequelae of reserpine therapy observed in this series were mild, as a general rule. Practically all 16 patients developed lassitude and lethargy of varying extent, though it was of greater magnitude with the larger doses. Another frequent complaint was nasal stuffiness which either disappeared spontaneously or responded to topical applications of a vasoconstrictor spray. On the other hand, severe mental depression occurred in two patients treated with the larger doses of reserpine. Suffice it to say that the symptoms disappeared in both cases when the dose was adjusted downward at a lower level. Finally, one patient succumbed to a severe upper gastrointestinal hemorrhage despite a negative history of a peptic ulcer and normal roentgen films of the alimentary tract.

ECG Effects: Except for the slowing of the ventricular rate, no instance of any constant specific electrocardiographic alterations was observed which could be construed as a reserpine effect. Harris[17] arrived at similar conclusions but observed more normal T waves in some of his patients' electrocardiograms. Conversely, Achor, Hanson and Gifford[21] noted improved electrocardiographic tracings in 7 of 21 patients

with left ventricular hypertrophy following therapy with rauwolfia drugs.

Summary and Conclusions

(1) Sixteen patients with organic heart disease who exhibited chronic atrial fibrillation and a rapid ventricular rate were treated with reserpine. The ventricular rate was significantly slowed in 12 of the 16 cases observed (75 per cent). There were four failures.

(2) Six case histories illustrating the effectiveness of reserpine in controlling this arrhythmia were presented in detail with electrocardiographic tracings taken both before and after rauwolfia therapy.

(3) The search for the minimal effective dose of reserpine in slowing the ventricular rate led to a reduction of the dosage in the early phase of this investigation. Thus, in our first few patients, the initial loading dose was 3 mg/day for three to four days followed by 0.75 mg daily thereafter. Subsequently, the drug was reduced to a 1 mg daily loading dose for a three to four-day interval followed by a maintenance level of between 0.25 to 0.5 mg once daily. This latter dosage formula proved to be far superior in achieving a bradycrotic response in all our remaining patients. Furthermore, the incidence of undesirable sequelae was proportionately reduced.

(4) The typical latent period of reserpine was demonstrated in this series and ranged between three to seven days. This was in accord with the pharmacologic properties of the drug. The possibility of potentiating the reserpine alkaloid with a digitalis glycoside, utilizing smaller doses of each component drug, was discussed.

(5) Mild side effects were encountered in all 16 patients and consisted of varying degrees of lassitude and drowsiness. Five patients developed nasal stuffiness. All these side effects were minimal and easily controlled. Severe mental depression was observed in two of our cases. This condition was remedied promptly by a reduction of the dosage. One patient succumbed to an intractable hemorrhage involving the upper gastrointestinal tract despite a negative history and absent roentgenologic findings of a peptic ulcer.

(6) In no instance in our series did reserpine revert the atrial fibrillation back to sinus rhythm. Nor did the electrocardiogram reveal any consistent characteristic alterations which could be attributable to the action of reserpine.

(7) The total number of patients in this study was too small to establish conclusively the bradycrotic value of reserpine in atrial fibrillation. Nevertheless, the results warrant a cautious optimism and suggest additional investigation of this drug as a worthy and promising endeavor.

(8) To the best of our knowledge, this is the first report in the literature apropos the bradycrotic effect of reserpine in a series of patients with organic heart disease and chronic atrial fibrillation with a rapid ventricular rate.

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Clinical Use of Quinidine in Atrial Flutter and Fibrillation*

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QUINIDINE was introduced to the medical profession as an antifibrillatory drug in 1918 by Frey.[1] Stimulated by Wenckebach's report[2] of successful conversion of atrial fibrillation with quinine, Frey studied related compounds. He concluded that quinidine was the most efficient drug for conversion of atrial fibrillation to sinus rhythm. This conclusion is still valid. He reported success in the conversion of 11 of 22 cases of atrial fibrillation.[1] It is of historical interest to note that several distinguished clinicians of the 19th century[3] recommended quinine for palpitation of the heart. In 1749 Senac[4] stated: "Long and rebellious palpitations have ceded to this febrifuge" (quinine). Levy,[5] and Eyster and Fahr[6] were the first in this country to report on quinidine as a cardiac drug.

Gold[7] lists the following disorders of cardiac rhythm in which quinidine is effective:

(1) Premature contraction or extrasystoles (auricular, nodal, ventricular).
(2) Paroxysmal auricular tachycardia.
(3) Nodal tachycardia.
(4) Auricular flutter.
(5) Auricular fibrillation.
(6) Ventricular tachycardia.
(7) Ventricular fibrillation.

Extrasystoles are usually benign manifestations. Except in situations of increased myocardial irritability such as infarction, they require no treatment. A recent study[8] of arrhythmias occurring with infarction has shown no increase in fatality in those having premature contractions. The ventricular dysrhythmias are now usually treated primarily with other antifibrillatory agents, such as procaine amide.[9] Quinidine in this fortieth year of its use in cardiology remains the drug of choice for conversion of atrial flutter and fibrillation to sinus rhythm.[7]

ACTION

Quinidine diminishes the rate and amplitude of contraction of isolated rabbit auricular strips until contractions cease.[10] It diminishes the uptake of oxygen in hearts of guinea pigs and rats.[11] Depression of the respiratory center occurs with suppression of respiration when quinidine is injected into the third ventricle of dogs.[12] In pig experiments ventricular fibrillation is inhibited following myocardial infarction produced by coronary ligation.[13] In man the amplitude and frequency of "f" waves in atrial fibrillation are diminished.[14] Slowing of "f" wave activity presages conversion; widening of the QRS, and ST and T wave changes indicate toxicity.[14]

Toxic Effects: Gastrointestinal effects with nausea, vomiting, and diarrhea are common, and moderate fall of blood pressure is the rule. Cinchonism is uncommon.[14] Other perilous complications include fever,[15] eczematous skin reactions,[16] thrombocytopenic purpura,[17] respiratory paralysis,[18] ventricular and atrial arrhythmias and peripheral embolization during conversion to sinus rhythm. Purpura is rare; only 28 cases have been reported to 1956.[17] Embolic phenomena occurring with conversion have been discussed since the time of Frey. Proved cases are very rare.[19]

CLINICAL USES OF QUINIDINE

Atrial Fibrillation: The most common use of

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quinidine today is the conversion of atrial fibrillation to sinus rhythm.[7] Fibrillation produces ineffective atrial contraction, tachycardia, and irregular ventricular beats. This diminishes cardiac output, increases venous pressure and circulation time, increases the heart size, and produces a variable pulse, blood pressure, and coronary flow.[20] The first consideration in untreated rapid fibrillation is the slowing of the rate, which is accomplished with digitalization. There is general agreement that this is the primary consideration in the therapy of atrial fibrillation. Difference of opinion exists as to which cases of digitalized fibrillators should go on to regulation with quinidine. DiPalma[21] lists indications and contraindications:

INDICATIONS AND CONTRAINDICATIONS OF QUINIDINE

Strongly Advised

1. Fresh auricular fibrillation or flutter with a normal roentgen heart shadow, and normal heart sounds.
2. Ventricular tachycardia.
3. Postthyroidectomy flutter or fibrillation.

Generally Accepted

1. Relatively old auricular flutter and fibrillation.
2. Ventricular premature beats.
3. Paroxysmal auricular or nodal tachycardia.
4. Auricular fibrillation occurring during myocardial infarction.

Often Given (Evidence in Favor Small)

1. Prophylaxis of arrhythmias in myocardial infarction.

Strongly Contraindicated

1. Complete heart block.
2. Bundle branch block or intraventricular conduction defect.
3. Subacute bacterial endocarditis.
4. Overdigitalization.

Generally Rejected

1. Congestive failure.
2. Auricular fibrillation which has replaced angina pectoris.
3. Hyperthyroidism with sinus tachycardia.
4. Markedly enlarged heart.
5. Severe mitral stenosis.

Often Rejected (Evidence of Danger Small)

1. Risk of embolism from auricle.
2. Rise in ventricular rate in auricular flutter.

Restitution of effective atrial contraction with conversion to regular rhythm has been stated to increase the cardiac output about 40 per cent.[22] Although regulation of atrial fibrillation has been shown to occur in 40 to 90 per cent of reported series of cases of persistent fibrillators, the relapse rate of fibrillation is high. Harris found only 20 per cent[23] of regulated fibrillators who continued their sinus rhythm as long as two years. Gold[7] states that quinidine is most effective in terminating paroxysmal atrial fibrillation. Patients with fibrillation in arteriosclerotic heart disease and in treated hyperthyroid heart disease are suitable candidates for conversion. However, in diseases in which the atria are more severely affected, as in severe mitral stenosis, regulation is more difficult and relapse to fibrillation is the rule.[24]

Atrial Flutter: In flutter, as in fibrillation, therapy is usually aimed at increasing the atrioventricular block and decreasing the ventricular rate with digitalis before regulation with quinidine as described below.

Dosage: Used as a prophylactic and for the maintenance of conversion to sinus rhythm, quinidine is usually given in doses of from 0.2 to 0.6 g. Conversion of atrial flutter and fibrillation usually follows therapeutic doses of digitalis or related compounds. There are many methods described. Quinidine may be given at hourly intervals during the morning on successive days according to Table I.

TABLE I

Schedule of Quinidine Therapy for Conversion of Atrial Fibrillation

8 a.m. (g)	9 a.m. (g)	10 a.m. (g)	11 a.m. (g)	Total daily dose (g)
0.2	0.2	0.2	0.2	0.8
0.4	0.2	0.2	0.2	1.0
0.4	0.4	0.2	0.2	1.2
0.4	0.4	0.4	0.2	1.4
0.4	0.4	0.4	0.4	1.6
0.6	0.4	0.4	0.4	1.8
0.6	0.6	0.4	0.4	2.0
0.6	0.6	0.6	0.4	2.2
0.6	0.6	0.6	0.6	2.4

This method achieves the blood concentrations (4 to 10 mg/*l*) necessary for conversion described by Sokolow and Edgar[25] and diminishes

the possibility of giving doses higher than are required. The patient should be hospitalized for therapy to have competent medical supervision available in case of complication. The drug is given in the morning during the time when hospital resident personnel are on the wards. The patient is observed before each dose. It is important not to give a dose after conversion has occurred.

Quinidine is a dangerous drug. The effective dose may also be the toxic dose and further increments must not be given. Doses in excess of 2.5 g in one day increase the dangers of toxicity. It is difficult to maintain regularity when large doses are needed. Ideally a daily electrocardiogram should be ordered to observe evidence of toxicity, other arrhythmias, and the conversion to sinus rhythm. Maintenance therapy with quinidine should begin the day following conversion and consists usually of 0.2 g to 0.6 g t.i.d.

These time-dosage schedules, of course, are not adequate for ventricular tachycardia. Rapid suppression of the ventricular pacemaker must be achieved. Gold[7] recommends 0.6 g every three hours until the ventricular rate has been retarded to 140 beats/min, the ventricular ectopic rhythm has vanished, or signs of drug toxicity appear.

Case Histories

The following cases illustrate some of the problems of quinidine therapy.

Case 1. S. R., a 75-year-old housewife, was admitted to Mt. Sinai Hospital in Minneapolis March 5 to April 1, 1954. She arrived dyspneic, orthopneic, and complaining of right pleural pain. Four years previously she had some chest pain and ECG changes interpreted as anterior myocardial infarction. She was fibrillating with a ventricular rate of 150. She was digitalized and the ventricular rate was reduced to 100.

On March 24, 2 g of quinidine were given in divided doses during the morning. At noon she was nauseated and vomited. That afternoon the ECG showed regular sinus rhythm at a rate of 96. Maintained on quinidine 0.2 g. b.i.d., she remained regular for the four years she has been followed. Admission chest x-ray showed a greatly enlarged heart with pulmonary congestion and a right-sided density thought to be pulmonary infarct. After digitalization the heart size diminished and again decreased slightly after regulation.

Summary: This patient represents a favorable result from quinidine therapy, remaining regular for over four years following her conversion to sinus rhythm. The atrial fibrillation probably resulted from the combination of her coronary disease and pulmonary embolism.

Case 2. W. W., a 43-year-old male farmer, was admitted to Minneapolis Veterans Hospital December 2 to December 18, 1957, with mitral stenosis and insufficiency. He had rheumatic fever in 1949 and was known to be fibrillating since 1953. He had several peripheral emboli. Auricular appendectomy and mitral commissurotomy were performed April 26, 1957. The surgeon noted moderate stenosis and insufficiency and he produced a small split of 3 mm in one commissure. The patient was not improved. A large heart was observed on x-ray before and after surgery. Quinidine was started December 13. The largest dose of 1.2 g was given on December 16 when the drug was discontinued because of widened QRS and runs of extrasystoles.

Summary: This is an example of an unsuccessful attempt at conversion of atrial fibrillation. The patient had a large heart. The primary heart disease was of the mitral valve. The fibrillation was long established. All these factors militated against the successful use of quinidine.

Case 3. B. J., a 54-year-old hospital employee, was admitted to Minneapolis Veterans Hospital November 25 to December 16, 1952. His symptoms of dyspnea, precordial pain, weakness, and irregular fast pulse appeared on the day of admission. He had previously had a diagnosis of aortic stenosis and insufficiency with atrial fibrillation and had been digitalized for the past year. He had the characteristic murmur and thrill of aortic stenosis as well as a diastolic basal murmur of aortic insufficiency. The blood pressure was 90/70. The heart was generally enlarged.

He was given 1 mg of digitoxin and converted to sinus rhythm with a maximum dose of 0.8 g of quinidine a day. However, he was unable to return to work after this hospitalization. He remained regular for at least one year but was fibrillating when next examined two years later. At that time a mid-diastolic apical murmur characteristic of mitral stenosis was evident. From the onset of his fibrillation he was a cardiac invalid. Chest x-ray showed generalized cardiac enlargement not reduced by regulation to sinus rhythm. Other views showed left atrial enlargement and calcification of both aortic and mitral valves at the time of his first admission. He died in 1957, five years after his first atrial fibrillation and decompensation. Autopsy was not done.

Summary: The clinical impression from the physical findings at the time of his admission

was aortic valve disease. The case shows that the mere presence of atrial fibrillation in aortic disease indicates the likelihood of mitral valve disease also. Typical findings of mitral valve involvement appeared later. The establishment of sinus rhythm persisted for at least a year but no clinical improvement resulted. The dynamic lesion was the aortic stenosis, notoriously refractory to therapy when decompensation occurs. The atrial fibrillation associated with the mitral valve disease was amenable to therapy but regulation did not alter the clinical picture.

Case 4. H. H., a 52-year-old male, was admitted to Minneapolis Veterans Hospital for the first time on August 8, 1953. Atrial fibrillation and congestive heart failure were present with physical findings typical of mitral stenosis and insufficiency. He had cardiac enlargement, pleural fluid, and dependent edema. After 1.2 mg of digitoxin his ventricular rate dropped from 160 to 90 (Fig. 1). He was maintained on digitoxin at 0.2 mg/day. Quinidine was given to a maximum of 0.8 g with conversion to sinus rhythm. He then showed gross T wave changes of drug intoxication; the P waves at the time of conversion were squared and notched. All therapy was discontinued and the P, ST, and T changes reverted to normal. The heart size, which was large with the fast fibrillation, diminished with the digitalization but did not diminish further with the quinidine regulation.

The duration of the sinus rhythm is unknown but he was readmitted February 3, 1954, with recurrence of dyspnea and atrial fibrillation. On this admission right heart catheterization showed no pressure abnormality. He was digitalized with 1.6 mg of digitoxin, diminishing his ventricular rate from 145 to 100. With quinidine given to a maximum of 0.8 g he converted to sinus rhythm. Again the heart was large with the fast fibrillation, contracted with digitoxin and did not change further with quinidine (Fig. 2). He left the hospital on maintenance doses of digitoxin and quinidine.

He remained regular at least six months but was readmitted with palpitation and dyspnea on February 3,

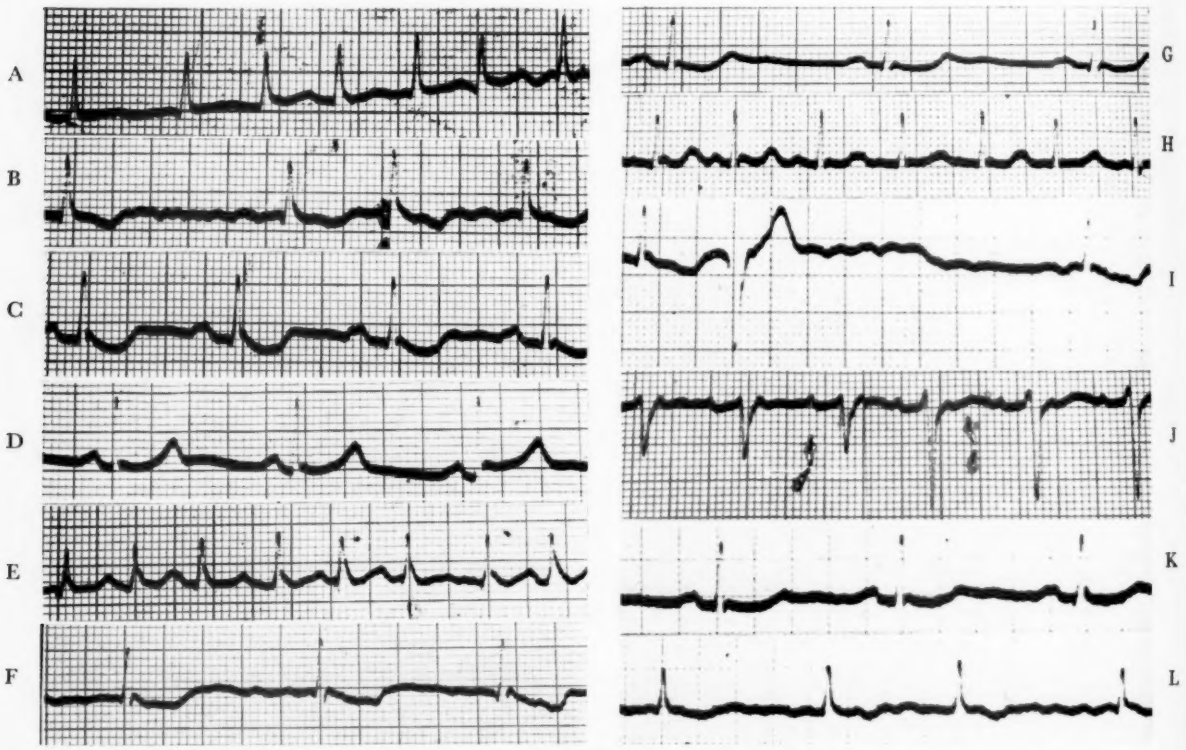

Fig. 1. Case 4. Lead 2 unless otherwise indicated. (A) 8-8-53: Fast atrial fibrillation on admission. (B) 8-11-53: Digitalized: slow fibrillation. (C) 8-29-53: After quinidine: regular rhythm with toxic P and T waves changes. Note square notched P. (D) 11-12-53: After two months without drugs: regular rhythm with disappearance of abnormal P and T changes. (E) 2-19-54: Second admission, fibrillating. (F) 2-25-54: Digitalized with toxic effects. (G) 3-5-54: Again regulated with quinidine; note abnormal P. (H) 2-3-55: Third admission, fibrillating. (I) 2-7-55: Overdigitalized, slow ventricular rate, ventricular premature beat. (J) 2-19-55: On digitoxin and quinidine. V_1 and V_2 showing atrial tachycardia with 2:1 block. (K) 2-21-55: Regular on quinidine 3 g; note abnormal P. (L) 5-24-55: Permanent atrial fibrillation.

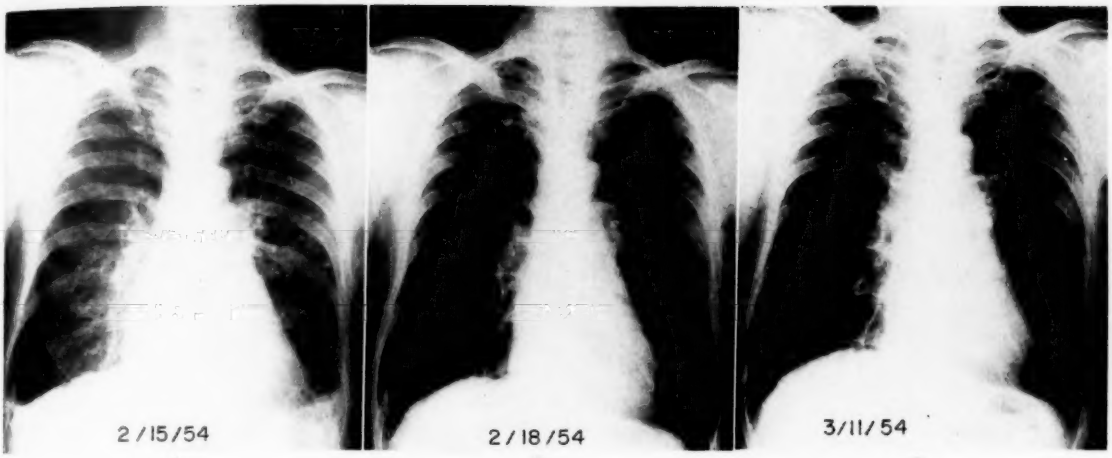

Fig. 2. Case 4. Chest x-rays on second admission. (A) 2-15-54: Large heart, pulmonary congestion and pleural fluid. (B) 2-18-54: Digitalized; heart smaller and lungs clear. (C) 3-11-54: Rhythm regular after quinidine but no further reduction in heart size.

1955. He was fibrillating and had an apical rate of 164. Cedilanid and digitoxin were given. The ECG on February 11, 1955, showed overdigitalization with deeply negative T waves and extrasystoles, and "f" waves at 450/min. On February 19 he developed paroxysmal atrial tachycardia with 2 : 1 block, atrial waves at 232/min. This occurred during maintenance of digitalis with 0.2 mg/day and quinidine of 1.4 g/day. On February 21, with a maximum dose of 3 g of quinidine, he became regular. He was found to be fibrillating again on May 24 and this irregularity has been permanent. Chest x-ray films showed the accordion changes in the heart size as before. He developed personality changes and eventually grand mal seizures very likely due to cerebral emboli.

Summary: A case of mitral stenosis was "successfully" converted to sinus rhythm on three occasions, illustrating the evanescent action of quinidine in mitral disease. Although conversion was accomplished the patient could not sustain his sinus rhythm with or without daily quinidine in maintenance doses. Paroxysmal atrial tachycardia with 2:1 block was a preliminary feature of one conversion episode. Abnormal P waves appeared with each regulation (Fig. 1). Long-term assessment indicates that quinidine failed to benefit the patient significantly.

Case 5. B. W., a 47-year-old carpenter, entered Minneapolis Veterans Hospital on January 2, 1956, and was discharged March 4, 1956. This patient had mitral stenosis and atrial fibrillation. He came into the hospital decompensated with a history of six weeks of dyspnea. Prior to that time he had done heavy work. Admission ventricular rate was 110/min (Fig. 3). He was digitalized and maintained on 0.1 mg of digitoxin a day. Activity of "f" waves was then 225/min and the ventricular rate 100.

Quinidine therapy was instituted on January 26. After 0.6 g he developed an atrial tachycardia with a 2:1 block, atrial rate 240, ventricular, 120. With the next dose of 0.2 g he reverted to sinus rhythm with notched P waves. Quinidine was maintained at 0.2 g four times a day and on January 31 he again had an atrial rhythm with 2:1 block with an atrial rate of 280, ventricular rate, 140. Quinidine was diminished to 0.2 g b.i.d. with the digitoxin remaining at 0.1 mg and the next day he had a regular sinus rhythm at a rate of 70.

He worked as a taxi driver for the next two years. The duration of his sinus rhythm is unknown but at his next follow-up April 29 he was found to be fibrill ting. The admission chest x-ray showed pulmonary congestion and cardiac enlargement which after digitalization diminished in size comparable to that seen on the x-ray prior to his fibrillation.

Summary: A patient with mitral stenosis entered the hospital decompensated with his first attack of atrial fibrillation. His conversion to sinus rhythm was attended by two episodes of atrial rhythm with 2 : 1 block (Fig. 3). With the largest dose of quinidine at the time of his first regulation abnormal notched P waves appeared. Two years later he was found to be fibrillating again after an unknown period of sinus rhythm.

Case 6. K. K., a 58-year-old farmer, was admitted to Minneapolis Veterans Hospital November 22, 1950, to

January 5, 1951. He had known of chest pain typical of angina pectoris for several years. Earlier that year he had been told by his private physician that he had atrial flutter. At the time of admission he developed severe left chest pain while walking and then became dyspneic and developed dependent edema. The blood pressure was 130/80. There were basal rales and the liver was enlarged. ECG showed atrial flutter with a 2:1 block, atrial rate of 270, ventricular rate of 135. Clinical diagnoses were: coronary sclerosis, angina pectoris, and atrial flutter.

He was digitalized with persistence of the flutter but increase of the block to 4:1 to 5:1. Quinidine was started on December 2. On December 7, with maintenance of the digitalization and quinidine increased to 1.2 g, atrial fibrillation was found with "f" wave of 375/min, ventricular rate of 60. At this dose of quinidine he converted the next day to sinus rhythm. No follow-up is available. Admission chest x-ray film showed considerable cardiac enlargement. The greatest minification occurred after digitalization. The heart was found to be only slightly smaller when the rhythm was normal.

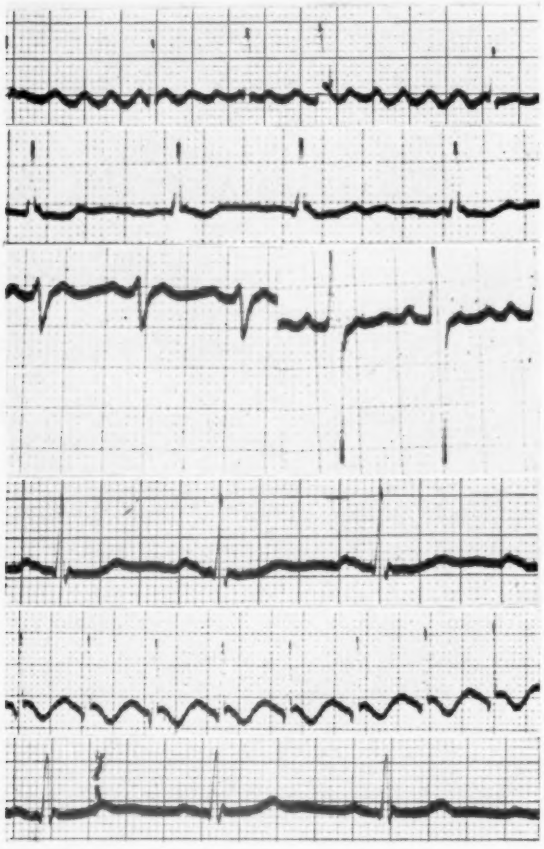

Fig. 3. Case 5. Lead 2 unless otherwise indicated. (A) 1-4-56: Fast atrial fibrillation on admission. (B) 1-25-56: Digitalized. (C) 1-26-56, 1 p.m.: After 0.6 g quinidine—atrial tachycardia with 2:1 block. Leads $V_{1, 2}$. (D) 1-26-56, 3 p.m.: After 0.8 g quinidine—regular rhythm. Note notched P waves. (E) 1-31-56: Quinidine and digitoxin maintained; atrial flutter with 2:1 block. (F) 2-20-56: Quinidine reduced; regular rhythm. P waves appear normal.

Summary: This is an example of a patient with coronary sclerosis with atrial flutter who was converted to atrial fibrillation with digitalis and quinidine and eventually with both drugs was converted to sinus rhythm. There was no follow-up.

Case 7. F. L., a 64-year-old man, was admitted to Minneapolis Veterans Hospital on July 18, 1952, and expired on August 9, 1952. His case has been previously reported.[18] The final diagnosis is idiopathic myocardial hypertrophy and fibrosis of unknown etiology. He was admitted decompensated with a fast atrial fibrillation. After digitalization he was started on quinidine; the second day with a dose of 1.6 g he showed T wave inversions in the chest leads. July 29 he received 1.6 g of quinidine. That evening he was found in a convulsive state, cyanotic, aphonic, and pulseless. He recovered in 15 minutes and had no neurologic residuals. He was thought to have had a cerebral embolus.

In spite of this he was given quinidine again and on 0.6 g on August 6 he converted to sinus rhythm. On August 7 he experienced a convulsion associated with cyanosis and absence of pulse lasting about 5 min, gradually returning to consciousness. Atrial fibrillation was then found. He was again given 0.6 g quinidine on August 8, 1952. Another episode similar to the August 7 event occurred during which an ECG was taken showing abnormal rhythm resembling a ventricular tachycardia. He died August 9. Chest film on admission showed an enlarged heart, pulmonary congestion, left pleural fluid. After digitalization the x-ray showed fairly normal lung fields and considerable reduction in heart size. The autopsy showed patent coronary vessels and patchy areas of fibrosis in the myocardium. The cerebrum was normal.

Summary: The patient had atrial fibrillation, heart failure, and myocardial hypertrophy of undetermined etiology. Following an unsuccessful attempt at regulation of atrial fibrillation with quinidine the patient was found in a convulsive, cyanotic, and pulseless state. Clinical diagnosis of cerebral embolus was suggested. The second attempt at quinidinization resulted in return to sinus rhythm and another convulsive episode similar to the first recurrence of fibrillation. With the third exhibition of quinidine an intractable tachycardia resulted. Failure to appreciate the syndrome of convulsions and apparent death as

a toxic manifestation of quinidine led twice to unwarranted resumption of quinidine therapy. The autopsy revealed no cerebral emboli.

Discussion

Quinidine is a potent antifibrillatory drug whose use is attended with significant danger. Finnegan[26] found one fatal and two severe reactions in 115 cases of atrial fibrillation treated with quinidine. Berman and Blumenthal[27] reported 5 deaths in 100 such cases. We observed the greatest improvement during the preliminary digitalis therapy with disappearance of the symptoms and signs of heart failure, slowing of the apical pulse, and greatest diminution of heart size as determined by chest roentgenogram.

In the six cases of atrial fibrillation reported here there were eight successful conversions to sinus rhythm out of nine attempts. One atrial flutter was successfully regulated. Of these seven cases, there were four of mitral disease including one with associated severe aortic stenosis, two of coronary disease, and one of idiopathic myocardial fibrosis and hypertrophy.

Paroxysmal atrial tachycardia with 2 : 1 block developed three times just prior to conversion to sinus rhythm. This arrhythmia, commonly associated with digitalis therapy,[28] seems to be potentiated by quinidine and presages the regulation. In two cases the P wave after conversion was distinctly abnormal with a squared notched appearance subsiding after discontinuance of digitoxin and quinidine.

One death presumably due to quinidine occurred in a patient with fibrillation who suffered two major neurologic complications during therapy just prior to and at the time of conversion to sinus rhythm. His death occurred during an intractable ventricular dysrhythmia. At autopsy no cerebral pathology and no emboli were found.

It is difficult to separate quinidine intoxication from other drug reactions. Quinidine for regulation of atrial arrhythmias is practically never given without preliminary digitalization. The hour of conversion is attended by the maximal dose of quinidine and associated with various arrhythmias and other complications. The difficulties are great enough to warrant hospitalization and hourly observation during regulatory therapy.

The ideal candidate for quinidine therapy has no organic heart disease, is fibrillating probably from extracardiac influences of temporary nature; his heart size after digitalization is not large; and, finally, he is still fibrillating after other cardiac therapy. A thyrotoxic patient still fibrillating after adequate antithyroid treatment and return to the euthyroid state approaches this ideal. Patients with coronary sclerosis respond favorably. Patients with mitral valve disease are more difficult to convert and often impossible to maintain regular.

Quinidine is abused by administration in large and repeated doses to fibrillating patients whose maximal benefit is already achieved by digitalization with the other features of a good cardiac regimen. This applies to patients with large hearts after digitalization, advanced mitral disease, and to those whose earlier quinidine "successes" had speedily relapsed into fibrillation.

Summary

Quinidine, after 40 years since its introduction by Frey as an antifibrillatory agent, is still the drug of choice for conversion of atrial flutter and fibrillation to sinus rhythm. It is effective in both supraventricular and ventricular arrhythmias. The suggested maximal dose orally in the adult is 2.5 g in one day in divided doses. The toxic dose may overlap the therapeutic dose. Toxic effects should be anticipated at the time of conversion. Quinidine regulation of arrhythmias calls for hospital management with daily electrocardiographic monitoring and clinical examination before each dose is given. Seven cases are presented illustrating problems in the use of quinidine. Three episodes of paroxysmal atrial tachycardia with 2 : 1 block occurred in two cases during quinidine therapy prior to conversion.

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Do's and Don'ts in the Treatment of Auricular Fibrillation with Quinidine*

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THERAPY should be based on an understanding of the pathophysiologic status of the ailment, a knowledge of the pharmacologic properties of the therapeutic agents to be employed, and an awareness of the fact that the dosage or extent of therapy should be governed by the patient's individual needs and clinical reactions.

Since reports continue to appear in the literature describing a relatively high incidence of shocklike syndromes, convulsions, and sudden and unexplained deaths in the course of, or following the use of, quinidine for the treatment of auricular fibrillation,[3,4] it was deemed almost mandatory to set forth a list of do's and don'ts founded on the principles formulated in the preceding paragraph.

USE OF QUINIDINE IN AURICULAR FIBRILLATION

Do's

(1) First digitalize the heart.
(2) Establish a maintenance dose of digitalis.
(3) Continue with digitalis maintenance dose.
(4) Begin treatment with a small dose of quinidine, and gradually increase the size and number of doses.
(5) Reduce size of quinidine dosage or discontinue its use at the first sign of toxicity.
(6) Be guided by patient's individual reaction to quinidine and need for the drug.
(7) Gradually reduce the daily dose of quinidine and establish a maintenance dose, once a normal cardiac rhythm is attained.
(8) Continue with daily maintenance doses of both quinidine and digitalis indefinitely.

Don'ts

(1) Begin treatment with quinidine before the heart is fully digitalized.
(2) Begin with large doses or frequently repeated large doses of quinidine, merely because the patient tolerates a test dose.
(3) Adhere to predetermined fixed schedules for quinidine dosage.
(4) Continue same size dose of quinidine when patient shows evidence of toxic symptoms.

Importance of Digitalization: Why is it so important first to digitalize the heart? A fibrillating heart is not a fully compensated heart. This has been well established. The cardiac metabolism is disturbed; the coronary flow is impaired; circulation is slowed; and the venous pressure is elevated. The cardiac efficiency is reduced from 15 to 80 per cent.[1] Therefore, it is imperative first to restore the heart to its optimal physiologic state before beginning the use of quinidine. This is done by the administration of digitalis. Another very weighty reason for first digitalizing the heart is that the better the heart is compensated, the more favorably it reacts to the depressant and therapeutic effects of quinidine. This means that less quinidine is required to obtain optimal clinical results. Occasionally restoration to normal sinus rhythm is accomplished by the use of digitalis only.

Dangers of Quinidine Administration: Why is it so important not to begin treatment of auricular fibrillation with quinidine, particularly chronic fibrillation with definite signs of heart failure? Since a fibrillating heart is already in a more or less depressed and embarrassed state, the addition of a powerful myocardial depressant, such as quinidine, is physiologically and pharmacologically unsound. It invites danger. Quinidine is a myocardial depressant. It inhibits myocardial metabolism. It is antagonistic to cardiac hormones, such as acetylcholine and actomyosin hormones probably responsible for initiation of the heart beat.

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Quinidine, too, is a respiratory depressant.[2] Patients with varying degrees of cardiac failure usually have some degree of respiratory difficulties. A depressed respiratory center is very sensitive to the toxic effects of quinidine. Cessation of respiration following the injection of quinidine is not an unusual occurrence in the experimental animal such as the cat and the dog; especially so, after administering the drug too rapidly or in too large a dose.[5] It is this toxic effect of quinidine which may be largely responsible for such serious complications as convulsions, shocklike syndromes, and unexplained sudden deaths that follow the misuse of this drug for the treatment of auricular fibrillation.

When and How to Administer Quinidine: When should quinidine be administered? Start quinidine therapy only after the heart has been digitalized and a maintenance dose of digitalis established and maintained.

How should quinidine be administered? It is of great importance to begin with small doses and gradually increase the size and number of doses. A patient may well tolerate a so-called test dose of 3 grains, but may suffer serious toxic effects if this same size dose or multiples of it are repeated too often over a short period.

Dosage Schedule: Every patient has his own therapeutic and toxic threshold to the effects of the drug. What may be a therapeutic dose for one individual may prove to be toxic for another. Some patients may require very small doses of quinidine for the restoration of a fibrillating heart to normal sinus rhythm, while in others unlimited amounts of the drug fail to have any beneficial effect. Treatment should never be based on any predetermined, fixed schedule of dosage. *Each dosage should be based on individual patient needs and reactions.* We have used the schedule in Table I with little change for some thirty years, but only as a guide, for administering quinidine.[6] It is flexible, relatively safe, and has proved to be effective in the treatment of auricular fibrillation.

Should any toxic symptoms appear, such as diarrhea, vertigo, nausea, vomiting, tinnitus, etc., slow down the schedule, i.e. revert back to the previous day's dosage for a period of a day or more. When the unfavorable symptoms disappear, resume schedule of dosage but at a slower rate. One may have to go back more than one day on the schedule before resuming treatment, or because of the patient's intolerance to the drug, it may be advisable to discontinue treatment entirely.

TABLE I

Daily Dosage Schedule of Quinidine Administration in Grams (and Equivalent Dosage in Grains)

Day	8:00 a.m. Gm (gr)	10:00 a.m.	12:00 Noon	2:00 p.m.
1	0.2 (3 gr)	—	—	—
2	0.2	0.2	—	—
3	0.2	0.2	0.2	—
4	0.2	0.2	0.2	0.2
5	0.33 (6 gr)	0.33	0.33	—
6	0.33	0.33	0.33	0.33
7	0.33	0.67	0.67	—
8	0.67 (10 gr)	0.67	0.67	—

Maintenance Dosage: Once the auricular fibrillation is restored to normal rhythm continue with that day's dosage for a few days, then gradually reduce the size and number of doses until a maintenance dose of quinidine is established. This amount is usually about 0.4 Gm, two 0.2 Gm doses daily, occasionally it may be 0.6 Gm, and not rarely, only 0.2 Gm. Continue this maintenance dose of quinidine and the digitalis maintenance dose indefinitely.

Do not give more than 2.0 Gm of quinidine in any one day. My experience has been that if more than 2.0 Gm of quinidine are necessary to successfully restore a fibrillating heart to normal sinus rhythm, the heart rate will not remain regular for any length of time and sooner or later it will revert to fibrillation.

Conclusions

Adherence to the do's and don'ts here presented not only affords a better method for treating auricular fibrillation but, more important, will help prevent the occurrence of such serious toxic complications as convulsions, shocklike syndromes, and sudden deaths as so often reported.

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Complete Atrioventricular Block Treated with Isoproterenol Hydrochloride*

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THE MANAGEMENT of the patient with Adams-Stokes attacks due to complete heart block is indeed a challenging problem. The many medications recommended certainly indicate the lack of effectiveness of any one preparation in the treatment of this often incapacitating illness. Therapy is usually directed either toward blocking the vagal cardioinhibitory action or by stimulating cardiac acceleration with sympathomimetic drugs in a manner similar to sympathetic discharge. The vagus has been shown to have only a minimal effect on the activity of the ventricles. Therefore, clinical attempts at amelioration of Adams-Stokes attacks by vagal inhibition are often not successful. Sympathomimetic drugs accelerate the idioventricular rhythm, but have as their drawback the fact that they may produce premature beats or other more serious ventricular arrhythmias as well as an increase in blood pressure.

A sympathomimetic amine capable of increasing the heart rate without the foregoing untoward effects would certainly be a welcome addition to the medical treatment of this disorder. The ideal therapy would be a single effective oral preparation. Nathanson and Miller[1–3] introduced the use of isoproterenol HCl in the treatment of complete heart block. We have repeated their acute studies and, in addition, have utilized the sublingual route for prolonged maintenance therapy in a group of cases with the Adams-Stokes syndrome due to complete heart block.

MATERIAL

Twelve men and one woman with complete heart block were studied. The age range was from 55 to 76 years. Seven patients had Adams-Stokes episodes and five required hospitalization. The period during which syncopal episodes occurred before isoproterenol HCl therapy was started varied from one day to twenty years. Three patients continued to have asystolic convulsions while under therapy with atropine, tincture of belladonna, aqueous and oily solutions of epinephrine and ephedrine, alone or in combination.

METHODS

Thirteen patients with complete heart block were given 15–20 mg of isoproterenol (Isuprel) HCl† sublingually. Serial electrocardiograms were taken every five minutes for the first hour and every fifteen minutes thereafter until the heart rate returned to control levels. Each of seven patients on separate occasions received subcutaneously 0.2 mg of isoproterenol HCl and 1.0 mg of epinephrine in order to compare the cardiac-accelerating effect of these two drugs. Serial electrocardiograms were taken every minute for fifteen minutes and then every five to fifteen minutes until control levels were reached.

Seven patients were studied on prolonged sublingual therapy. Doses varied from 10 mg every two hours to 20 mg every three hours. The medication was taken only during the waking hours.

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† Supplied through the courtesy of the Medical Research Dept., Winthrop Laboratories, New York.

Results

ACUTE STUDY

Seven of the thirteen patients given the sublingual preparation had a significant acceleration in idioventricular rate (Table I). A response was considered significant when the cardiac rate after medication exceeded the control rate by at least ten beats per minute. In these seven patients the average interval before this significant increase in rate occurred was 21 minutes. The average interval before the peak rate was reached was 39 minutes (range 30–58), and the average rate at this time was 51 beats per minute. The average duration of action after the time of onset of the response was 86 minutes. The average rise from control levels to the maximal rate was 18.7 beats per minute (range 12–33).

TABLE I

Average Response of Cardiac Rate to Isoproterenol and Epinephrine in Patients with Complete Atrioventricular Block

	Isoproterenol		Epinephrine, subcutaneous
	Sublingual	Subcutaneous	
Significant response (no. patients)	7 of 13	7 of 7	5 of 7
Control rate	33	33	33
Onset (min)	21	4.1	25
Peak time (min)	39	8	45
Peak rate	51	58	62
Duration (min)	86	72	74

Five of the six patients who did not respond to the 15 mg dose also failed to respond to 20 mg. One patient who failed to respond to smaller doses reacted to 25 mg with a slight increase in rate.

All of seven patients given 0.2 mg isoproterenol subcutaneously had a significant response. In four of these seven the heart rate had not increased after the sublingual test dose. The average time of onset of this response was 4.1 minutes (range 2–7). The maximal rate was reached at 8 minutes (range 7–20). The average duration of action was 72 minutes (range 28–144). The average peak heart rate was 58 beats per minute (range 45–96). The average increase in rate above the control level was 25 beats per minute.

Seven patients received 1.0 mg epinephrine subcutaneously. Five had a significant response. The average time of onset was 25 minutes (range 15 to 60). The peak rate, averaging 62 beats per minute, occurred after an average of 45 minutes (range 20–48). The duration of activity from the time of onset until control rates were reached averaged 74 minutes (range 15–135). The average increase in rate from control levels to the point of maximum stimulation was 29 beats per minute. Only one patient (case 4) had a better response to epinephrine than to subcutaneous isoproterenol.

A comparison of the effect of these two drugs on the heart rates of the first six patients in this series is shown in Figure 1.

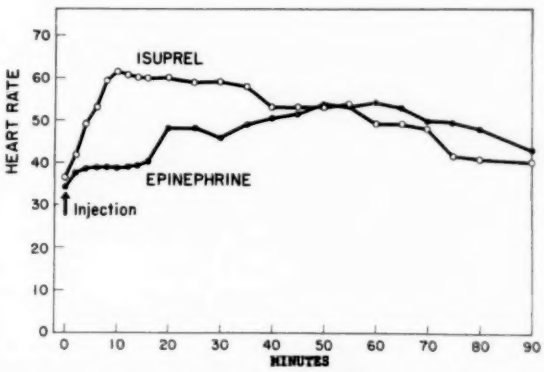

Fig. 1. Comparison of average effect in 6 patients given a single subcutaneous dose of isoproterenol (0.2 mg) and epinephrine (1.0 mg).

PROLONGED STUDY

Seven patients with Adams-Stokes episodes were treated with sublingual isoproterenol HCl for periods from three and one-half days to nine months. In only one patient (case 3) was it necessary to change to the parenteral form of the drug because of failure of sublingual administration to prevent asystolic convulsions. The remaining six patients had no further Adams-Stokes episodes while receiving adequate doses of the medication sublingually. In four of these cases the Adams-Stokes attacks reappeared when the medication was discontinued or administered at less frequent intervals. Three

of these patients initially received other medication for periods of from one to five weeks but continued to have convulsions. During the subsequent sublingual administration of adequate doses of isoproterenol no such attacks occurred.

Case Histories

Case 1. W. F., a 70-year-old Negro male, was admitted with a pulse rate of 10–12 beats per minute and was having convulsions in the supine position. Electrocardiograms revealed complete atrioventricular block.[5,6,15] The response to one 20 mg sublingual dose of isoproterenol was prompt, with acceleration of the heart rate to 30–35 beats per minute. Continued sublingual therapy with 20–30 mg at three-hour intervals maintained a cardiac rate of 30 to 60 beats per minute. He became more alert and had no further convulsions. This improvement in heart rate and clinical condition continued for eight days when a sudden severe upper gastrointestinal hemorrhage resulted in death.

Case 2. J. N., a 67-year-old white male, had experienced infrequent Adams-Stokes episodes for twenty years. Atropine and ephedrine seemed to control these attacks until two weeks prior to admission when they became more frequent, necessitating hospitalization. The electrocardiogram revealed complete heart block.

During the week of control therapy with atropine and an oily preparation of epinephrine the patient had no asystolic convulsions. When these medications were discontinued the convulsions recurred. Isoproterenol was then begun in a dose of 10 mg sublingually every two hours, and no convulsion occurred for a period of three and one-half days. The inadvertent omission of this medication for a 24-hour period was responsible for another series of asystolic convulsions which were not abolished by aqueous epinephrine. The patient died in one of these episodes.

Case 3. J. W.,[4] a 55-year-old white male, was admitted in cardiac decompensation with a heart rate of 28 per minute. He had suffered one episode of syncope two weeks prior to admission. There was no recurrence prior to entrance or during the initial eleven days of hospitalization. Electrocardiograms showed complete atrioventricular block.

On the twelfth day a series of asystolic convulsions began which continued over a period of sixteen hours. These could not be controlled by the routine medications or by the usual sublingual doses of isoproterenol. An electrical cardiac stimulator was then used, with immediate restoration of rhythmical cardiac contraction. An intravenous infusion of 1.0 mg isoproterenol in 200 ml of 5% glucose in water was then started at a rate of 5 μg per minute. When the stimulator was turned off 20 minutes later the patient's heart contracted spontaneously at a rate of 44 per minute and continued to do so during the remainder of the isoproterenol infusion. Twenty minutes after the infusion had been completed the heart rate began to slow. The patient had another asystolic convulsion 32 minutes after termination of the infusion. A second infusion, which supplied 3 μg isoproterenol per minute, maintained the ventricular rate at between 44 and 48 beats per minute except for a brief episode of asystole that responded to the cardiac stimulator. One milligram isoproterenol was then given intramuscularly every hour for 22 hours without further seizures. The pulse rate was maintained at 40 beats per minute during this period. Cardiac decompensation then recurred but responded to intensified treatment. Isoproterenol was begun sublingually in a dose of 20 mg every hour, and for five hours no Adams-Stokes episodes occurred. Acute severe cardiac decompensation again supervened, with resultant death.

Case 4. W. Hrt., a 71-year-old white male, was admitted for an inguinal herniorrhapy, and while recovering from this operation began to have occasional syncopal attacks. He was transferred to the medical service, where asystolic convulsions continued intermittently despite atropinization. The electrocardiogram revealed complete heart block.

After a series of asystolic convulsions, isoproterenol was begun sublingually in a dose of 15 mg every three hours. Because of discomfort from palpitation the dose was reduced to 10 mg every two hours during waking hours (upward shift of ventricular pacemaker shown in Figure 2). In subsequent electrocardiograms the degree of atrioventricular block decreased from a 2:1 ratio to delayed conduction without dropped ventricular beats.[16]

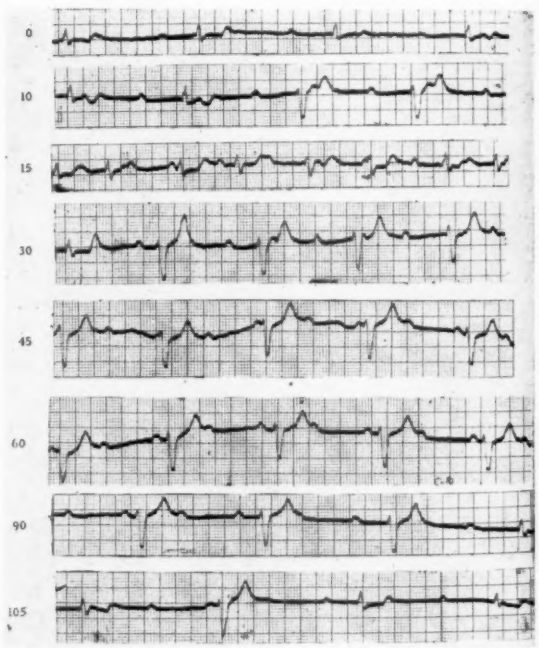

Fig. 2. Case 4. Response to 15 mg isoproterenol HCl sublingually for a period of 105 minutes (numbers at left show minutes). Note increase in ventricular rate and upward shift of ventricular pacemaker.

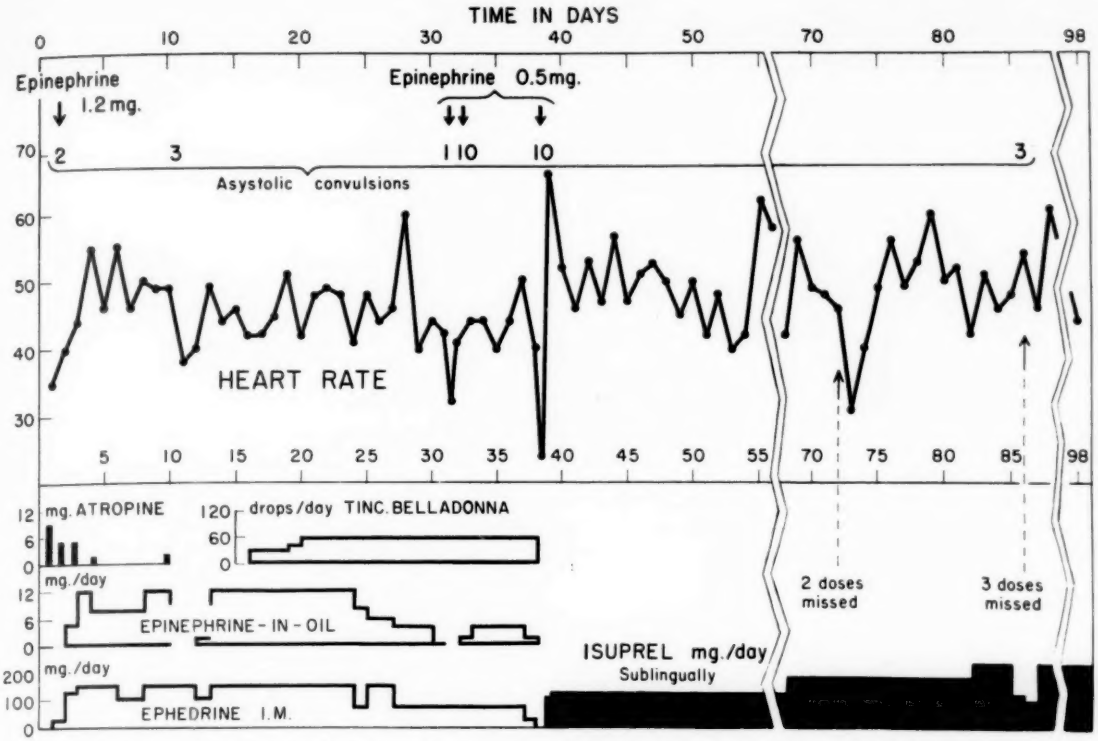

Fig. 3. Case 5. Effectiveness of sublingual isoproterenol HCl in the treatment of the Adams-Stokes syndrome.

During the next six months there were no further Adams-Stokes attacks. A bilateral cataract removal was performed at this time without difficulty. He was later rehospitalized with moderately severe cardiac decompensation and responded poorly to the usual regimen for cardiac failure. Due to the slow idioventricular rate in association with his complete heart block the isoproterenol was increased to 15 mg every two hours with minimal cardiac acceleration. About 90 minutes after a dose of isoproterenol a convulsion, not accompanied by a period of asystole, occurred. The electrocardiogram at that time showed a "slow" ventricular tachycardia (80–90). This continued throughout the night. The cardiac decompensation became increasingly severe, resulting in death 14 hours after the sudden change in his condition.

Case 5. W. Hmn., a 76-year-old white male, was brought to the hospital because of convulsions. Physical examination revealed a pulse of 26 to 40 per minute. Jerking spasmodic motions of both legs were noted. Electrocardiograms on different occasions revealed complete atrioventricular block. His response to combined therapy for heart block with ephedrine, atropine, and epinephrine-in-oil was rather slow. Epinephrine-in-oil was discontinued on the seventh day, and on the tenth day a series of asystolic convulsions occurred. The reinstitution of epinephrine-in-oil accelerated the heart rate to between 40 and 48 beats per minute and he remained asymptomatic until one month after admission, when the epinephrine-in-oil was again stopped. Although ephedrine and tincture of belladonna were continued, another series of asystolic convulsions commenced that could not be adequately controlled with aqueous epinephrine. Despite the reinstitution of epinephrine-in-oil the convulsions continued throughout the night.

Five weeks after admission asystolic convulsions recurred and were uncontrolled for 24 hours by the usual medications. Sublingual isoproterenol was started at this time in a dose of 15 mg every three hours. The response was excellent (Fig. 3), and the electrocardiogram the next morning showing complete heart block with a ventricular rate of 60–72 per minute. No convulsions or periods of asystole occurred during the next seven weeks. Inadvertently three consecutive doses were then omitted resulting in three convulsions. Isoproterenol was reinstituted and continued in a dose of 20 mg every two hours. No convulsions or episodes of syncope occurred during the next five weeks. He died from severe cardiac decompensation three months after the start of isoproterenol therapy.

Case 6. E. L., a 65-year-old Negro male, had been treated without success for his dizzy spells over a period of three years on an outpatient basis. These spells occurred three or four times per day. His heart rate was 30 to 36 beats per minute on frequent determinations. The electrocardiogram revealed a complete heart block.

Although the test dose of sublingual isoproterenol did

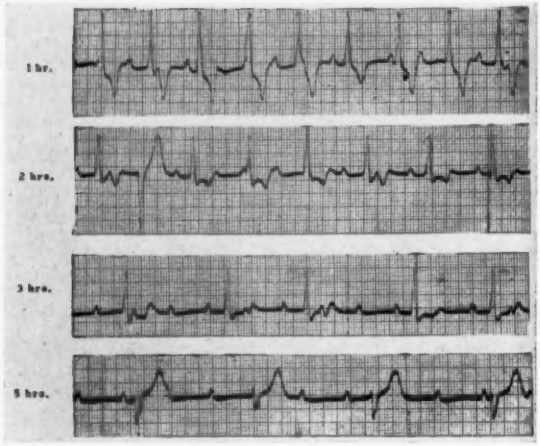

Fig. 4. Case 1. Development of "slow" ventricular tachycardia after inadvertent subcutaneous administration of 20 mg isoproterenol HCl, with spontaneous reversion to former rate.

not produce a significant response, it was decided to treat him with 20 mg every two hours to observe the effect on the Adams-Stokes episodes. Only one or two mild dizzy spells have occurred during nine months of isoproterenol therapy despite the fact that the heart rate has increased only slightly (40 per minute).

Case 7. N. M., a 63-year-old white male, was admitted to the hospital because of heart failure. The electrocardiogram revealed a rate of 28 beats per minute and complete atrioventricular block. Maintenance therapy with isoproterenol was begun with a dose of 20 mg every two hours with resultant increase in the heart rate from a level of 28–30 per minute to one of 40–50.

On his first visit to the outpatient department he complained of frequent episodes of dizziness and lightheadedness which initially were attributed to heart block. Careful questioning of the patient revealed that he had not correctly understood the instructions and had been taking two tablets three times per day instead of every two hours. He was reinstructed in the use of the drug and has not had any episodes of dizziness for a period of twenty weeks.

Side Reactions and Toxicity

Side reactions to sublingual isoproterenol were few, considering the frequency and size of the doses. Two patients had palpitations after receiving 15 mg, but when the dose was reduced to 10 mg given more frequently this complaint was eliminated without detracting from the effectiveness of the medication. One patient developed a sore mouth which disappeared while the medication was continued at the usual dosage and interval.

The majority of the patients receiving subcutaneous epinephrine or isoproterenol complained of uncomfortable palpitations at the height of action of the drug. Only one was vociferous in his complaints.

One patient (case 1) inadvertently given 20 mg of isoproterenol subcutaneously developed a "slow" ventricular tachycardia (Fig. 4). The rate gradually returned to the pretreatment level in about five hours without any untoward effect on the patient. Patient J. W. (case 3), who was purposely given 2 mg subcutaneously, also developed a "slow" ventricular tachycardia. The original focus regained control of the heart at the former rate in about fifty minutes.

Discussion

Complete heart block is always associated with the danger of ventricular arrhythmia or standstill and resultant death. The change from one focus to another, the firing off of a rapid run of ventricular beats, either as tachycardia or as fibrillation,[8,9] or the transient or final loss of initiative ability of the myocardium results in a disturbing situation of varying severity called the Adams-Stokes syndrome. The treatment of this condition leaves much to be desired, and one is never certain that the patient will not escape from what appears to be good control of the disorder. The multiplicity of medications[1,7] advocated indicates the lack of effectiveness of any drug or combination of drugs heretofore used.

Comparison of Isoproterenol and Epinephrine: Subcutaneous isoproterenol HCl is five times as effective as an equal dose of epinephrine in increasing the ventricular rate of patients with complete heart block. All of our patients given isoproterenol subcutaneously had a substantial increase in cardiac rate, but that was true of only 70 per cent of the patients given epinephrine. Those who responded to both medications had better results with isoproterenol despite the fact that the dosage of the latter was one-fifth that of epinephrine.

Nathanson and Miller[1,2] tested patients with complete heart block in much the same way as we did, with identical results. They felt that isoproterenol HCl raises the level of the focus

in the treelike conducting tissue and that epinephrine tends to lower this focus. Our results suggest that both are capable of raising the level of the controlling focus. In the occasional case in which epinephrine appeared to lower the focus, as shown by an increase in the number of ventricular extrasystoles, isoproterenol did not produce this undesirable effect. Bizarre ventricular complexes and occasional runs of ventricular tachycardia were more frequent with therapeutic doses of epinephrine than with isoproterenol. A pressor effect was observed when the former drug was used but was absent or negligible with the latter.

The safety of isoproterenol HCl has been shown in many animal studies.[10–14] One of our patients (case 1) inadvertently received subcutaneously one hundred times the recommended dose of isoproterenol HCl. He responded with a "slow" ventricular tachycardia. In five hours the original focus was again in control. One can speculate as to the result if one hundred times the recommended dose of epinephrine had been given.

Sublingual versus Subcutaneous Isoproterenol: The sublingual dose of 15 to 20 mg isoproterenol HCl used in this series was effective in 54 per cent of those tested. Patients would either respond by significant increase in heart rate to this dose or not at all. Nathanson[1] had a 50 per cent incidence of response and came to the same conclusion. Unlike the sublingual route, the subcutaneous route produced a significant rise in heart rate in every patient in this series even though they had had no response to the sublingual dose. The time of onset for the subcutaneous route was faster in our series (average four minutes) than it was in Nathanson's (average twelve minutes), and the durations of action in our group was longer (average 72 minutes versus 58).

Subcutaneous administration of isoproterenol HCl is more consistently effective than sublingual but suffers from the drawback that frequent injections are required. Oral therapy, if it were as reliable, would be preferable.

Increase in the cardiac rate was much more delayed after subcutaneous epinephrine than after isoproterenol, probably because of delayed absorption of the former, the result of local vasoconstriction. Isoproterenol, a vasodilator, permitted rapid absorption. Only five out of seven patients given epinephrine had a significant response, once action had begun. Subcutaneous isoproterenol was ten times faster in producing a rise in rate and three times faster in reaching the peak rate, and its effect lasted as long as that of epinephrine.

Although sublingual isoproterenol HCl does not increase the cardiac rate in some cases with heart block, it may decrease the incidence of Adams-Stokes episodes. While conclusions cannot be drawn from one case, it is of interest that the heart rate of patient E. L. (case 6) was not significantly increased by sublingual administration of the drug, yet during a nine-month period of treatment Adams-Stokes attacks did not occur. Although the drug did not accelerate the rate, there may have been sufficient activation to prevent slowing of the rate.

Intravenous Infusions: Our experience with the intravenous administration of isoproterenol HCl is limited to one patient (case 3), who was given infusions on two separate occasions during periods of severe Adams-Stokes Syndrome. Only one asystolic convulsion, which was precipitated by exertion, occurred during the course of these infusions. Recovery from the asystolic convulsions was much faster during the infusion than before or afterward.

Summary and Conclusions

(1) Sublingual isoproterenol HCl is effective treatment for Adams-Stokes attacks due to complete heart block. All patients receiving long-term maintenance therapy were markedly improved.

(2) Fifty-four per cent of the patients in this series had a significant increase in cardiac rate in response to a sublingual test dose of 20 mg isoproterenol HCl.

(3) Subcutaneous isoproterenol increases the heart rate sooner, reaches a peak faster, and lasts as long as a five-times-larger dose of subcutaneous aqueous epinephrine.

(4) Intravenous infusion of isoproterenol appeared to be effective in maintaining the heart rate in the one case in which it was used.

(5) Isoproterenol will raise the basic focus in some patients, stimulate the basic focus in

the remainder, and rarely, if ever, lower the pacemaker. Epinephrine will usually do the same, but occasionally it lowers the focus.

(6) Amounts of subcutaneous isoproterenol five, ten, and one hundred times the recommended dose were given without untoward effects, thus indicating a wide margin of safety.

(7) Six of seven patients with the Adams-Stokes syndrome due to complete heart block were maintained for an average of 113 days without convulsions or syncopal attacks by the sublingual administration of 10 to 20 mg isoproterenol at intervals of two or three hours.

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Bidirectional Tachycardia*

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BIDIRECTIONAL tachycardia is an uncommonly reported cardiac arrhythmia the occurrence of which is usually of grave prognostic significance. Thirty-six cases have been reported formally in the literature,[1,2] but this does not include other cases which have been described in standard textbooks.[3,4] Although the first reported clinical description was published by Schwensen[5] in 1922, bidirectional tachycardia had been produced experimentally by Levy and Lewis[6] in 1911 using dogs who had inhaled chloroform vapor. Since 28 of the 36 reported patients died within a short time after the onset of the arrhythmia, the serious nature of this abnormal rhythm is readily apparent.[2,7]

The clinical occurrence of the arrhythmia is usually associated with severe organic heart disease.[1] Auricular fibrillation has been a frequent antecedent rhythm. Thirty of the 36 reported patients were receiving digitalis at the time of onset, but it is evident that digitalis alone, even in very large doses, does not give rise to bidirectional tachycardia unless advanced myocardial damage is also present. The amounts of digitalis administered in the reported cases generally have not been excessive under usual circumstances. Paroxysms of bidirectional tachycardia have also been reported following the administration of calcium salts[8] and during the course of nicotine intoxication.[9]

The occurrence of bidirectional tachycardia is usually unsuspected clinically, and the diagnosis depends upon the recognition of the electrocardiographic pattern. Two QRS configurations alternate rhythmically, but the complexes are not necessarily inscribed in opposite directions in each lead. The term "variform conduction of the QRS complex" as used by Scherf and Kisch[10] seems to be a suitable description. Not all of their cases, however, demonstrated the striking alternating nature of the QRS complex which is present in the type of arrhythmia which we are reporting. Other types of conduction and rhythm disturbances such as bigeminal rhythm due to ventricular premature contractions, and intermittent bundle branch block or Wolff-Parkinson-White conduction may also cause confusion because of their electrocardiographic resemblance to bidirectional tachycardia, but careful examination of the record will usually lead to the correct diagnosis.

Rate and Regularity of Rhythm: The reported cases of bidirectional tachycardia show some variability in rate, regularity, and QRS duration time. The rate is usually about 150/min, counting both complexes. Although the rhythm may be regular, the interval between the first type of complex and the second type of complex may vary constantly by as much as 0.04 second from the succeeding interval between the second and the first one. The distance between complexes of the same configuration is usually constant. In some cases it is difficult to measure the distance accurately between the QRS complexes because of their configuration. The QRS duration is normal in some instances and prolonged in others.

Mechanisms of Production: Since bidirectional tachycardia may represent a heterogeneous group of cases with similar electrocardiographic configurations, it is not surprising that several different mechanisms for its production have been proposed. One of the

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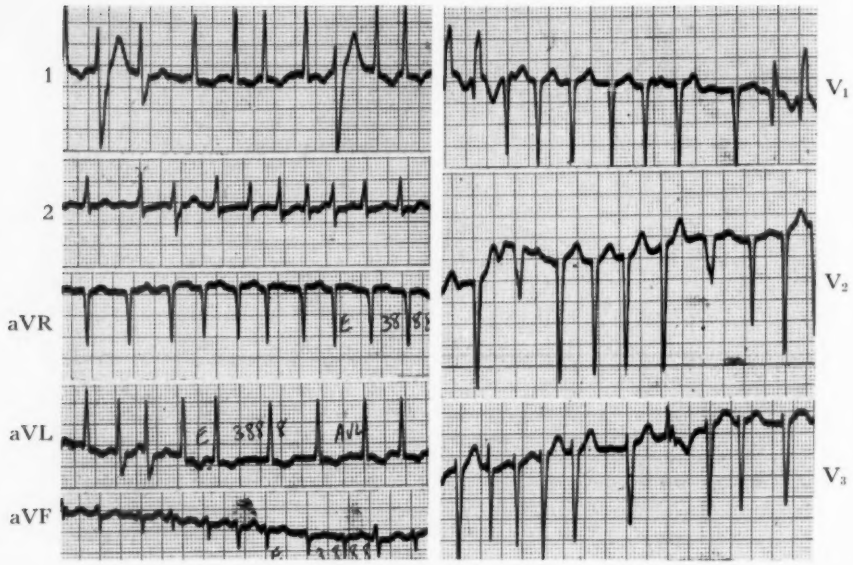

Fig. 1. Case 1. Electrocardiogram taken before onset of bidirectional tachycardia. Auricular fibrillation is present with rapid ventricular response and ventricular premature contractions.

earliest theories suggested that the complexes are ventricular in origin and that this arrhythmia represents a form of ventricular tachycardia.[5,11] This theory was based on the observation that most of the cases show many ventricular premature contractions prior to the onset of bidirectional tachycardia, and that experimentally produced bidirectional tachycardia is also associated with the occurrence of many ventricular premature contractions. It was generally considered that two foci of impulse formation are functioning, one in each ventricle. As another possibility, several authors suggested that a single focus may be operating above the bifurcation of the bundle of His, and that the bidirectional form of the QRS complex is due to alternate conduction through the right and left branches.[11,12]

White and Palmer[13] rejected the idea that a single focus above the bifurcation of the bundle of His is present because of the previously noted observation that there may be some irregularity of rhythm and alternation of the time interval between complexes. They proposed that a double ventricular circus movement is responsible. Scherf and Kisch, however, concluded that a single focus of impulse formation is present which could explain the findings in their cases, including the irregularities in rate.[10]

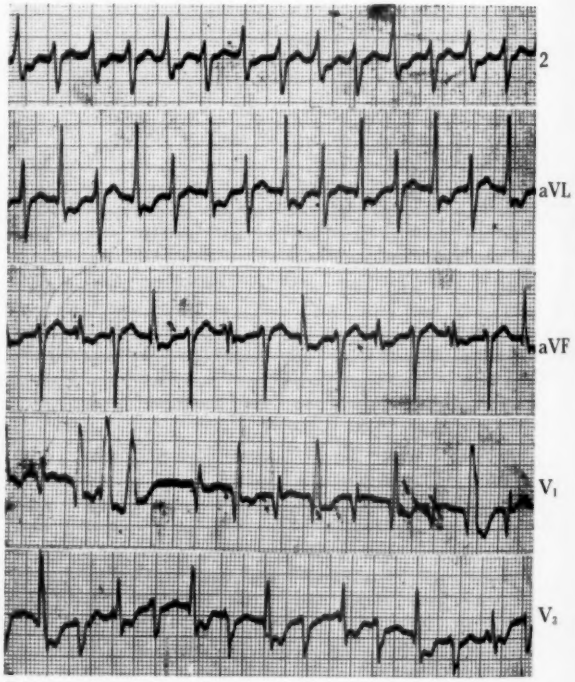

Fig. 2. Case 1. Bidirectional tachycardia before treatment with EDTA.

Further evidence for a supraventricular focus was presented by Zimdahl and Kramer,[1] who

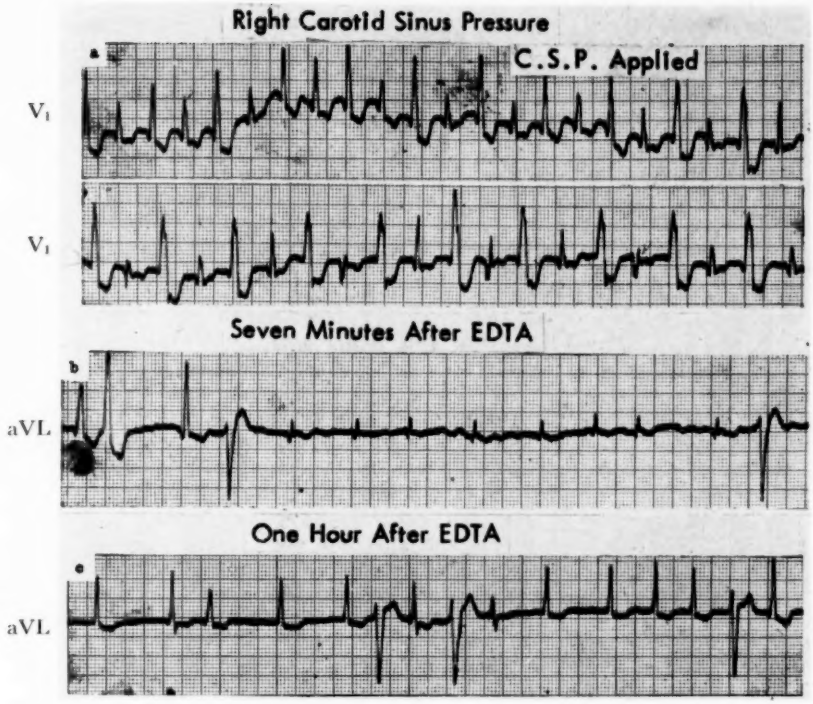

Fig. 3. Case 1. (A) Bidirectional tachycardia. Rate is slowed by carotid sinus pressure. (B) Disappearance of bidirectional tachycardia during EDTA infusion, with reappearance of auricular fibrillation. (C) Auricular fibrillation present 1 hour following EDTA infusion.

showed that one of the two complexes in their case could be abolished by carotid sinus pressure, indicating that at least one of the QRS complexes was initiated by a focus above the ventricles which was under vagal influence. Incorporating the previous proposals of ventricular and supraventricular foci, they suggested that two foci are present—one above the bifurcation of the bundle of His and one within the ventricles. More recently Velasquez and Kelser[2] were successful in abolishing this rhythm with vagal stimulation by using the Valsalva maneuver, again demonstrating the supraventricular nature of the site of impulse formation. In a recent case report, Hellman and Lind[7] have also concluded that the site of the impulse formation is above the bifurcation of the bundle of His.

We have recently observed two cases of bidirectional tachycardia, one of which was successfully treated by calcium chelation with sodium ethylenediamine tetraacetic acid (EDTA).

Case Histories

Case 1. M. Z., a 69-year-old-white female, was admitted to the Jewish Hospital of St. Louis for the fourth time on September 30, 1957, because of severe congestive heart failure. The patient had been treated for cardiac decompensation which was first noted in February, 1954. She was very obese and known to be hypertensive for many years. The electrocardiogram had previously shown left ventricular enlargement and frequent multifocal ventricular premature contractions. Although sinus rhythm was usually present, auricular fibrillation had been noted on several occasions. Because of the patient's failure to cooperate, digitalis had been discontinued and the patient was being treated with weekly injections of mercurial diuretics. For three weeks prior to admission, dyspnea and orthopnea had become increasingly severe.

Physical examination revealed the blood pressure to be 160/100. Fine moist rales were present at both lung bases and the liver edge was palpable 6 cm below the right costal margin. There was 2 plus pitting edema of the ankles and feet. The electrocardiogram showed auricular fibrillation with rapid ventricular response (160–170/min) and frequent ventricular premature contractions (Fig. 1).

The patient was initially given 1.0 mg of Lanoxin intravenously followed by 0.5 mg of Lanoxin intra-

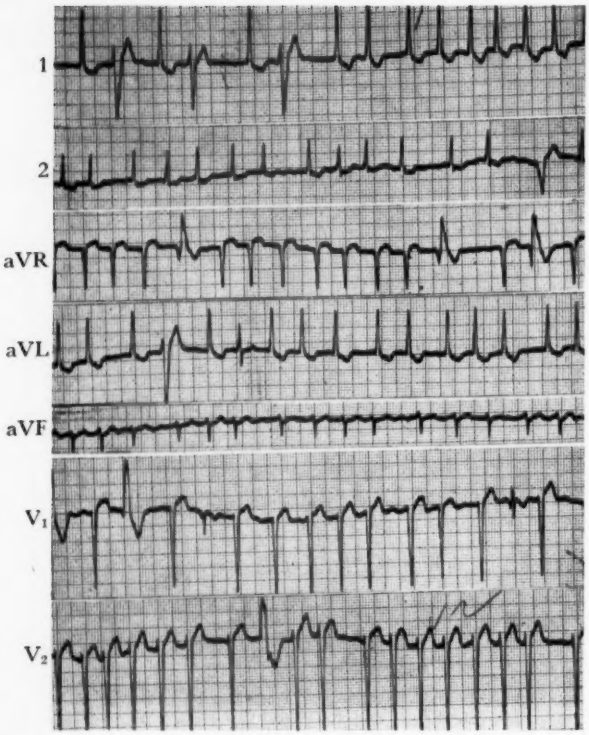

Fig. 4. Case 1. Record taken 10 days after onset of bidirectional tachycardia. Auricular fibrillation is present with rapid ventricular response and ventricular premature contractions.

muscularly three hours later. On the following day the patient appeared to be less dyspneic. Electrocardiogram revealed bidirectional tachycardia (Fig. 2). Right-sided carotid sinus pressure resulted in slight slowing of both types of ventricular complexes (Fig. 3A). Because of the suspicion that digitalis intoxication might be present, a solution of 3 g of trisodium EDTA mixed with 400 cc of 5 per cent glucose in water was given intravenously. The infusion lasted 30 minutes. The electrocardiogram taken 7 min after the beginning of the infusion showed auricular fibrillation with frequent ventricular premature contractions (Fig. 3B). Auricular fibrillation persisted throughout the infusion and remained thereafter (Fig. 3C). Following the administration of the trisodium EDTA, the patient appeared to be much improved. The serum calcium level fell from 8.1 to 7.2 mg/100 ml during the infusion. Digitalis was then discontinued for several days. The rhythm continued to be auricular fibrillation with many ventricular premature contractions (Fig. 4).

Subsequently the patient was treated with varying amounts of digitalis and on November 20, 1957, quinidine was given and sinus rhythm returned. The patient was maintained in a fair state of cardiac compensation until her sudden death on February 1, 1958. Permission for postmortem examination was not granted.

Case 2. G. P., a 72-year-old white male, was admitted to the Jewish Hospital of St. Louis for the eighth time on December 20, 1955. He had been suffering for many years from hypertensive cardiovascular disease and congestive heart failure which was treated with digitalis and periodic injections of mercurial diuretics. He had received ganglionic blocking agents, hydralazine, and reserpine without a consistent reduction in blood pressure. Although his electrocardiogram had previously shown left ventricular enlargement, a record taken in September, 1955, showed left bundle branch block with increased P-R interval. For about three weeks prior to admission the patient had noted increasing dyspnea and weakness.

Physical examination revealed the blood pressure to be 200/120. The patient was in obvious respiratory distress and the neck veins were distended. The point of maximum impulse was in the 6th intercostal space at the anterior axillary line. A soft blowing systolic murmur was heard at the base. The lungs were clear. The liver was palpable 6 cm below the right costal margin. No peripheral edema was present. Urinalysis revealed 3 plus proteinuria and the specific gravity was 1.017. Examination of the blood revealed the hemoglobin to be 10.4 g/100 ml. The blood urea nitrogen was 66 mg/100 cc, and the serum potassium was 4.8 meq/l. The admission electrocardiogram showed left bundle branch block, sinus rhythm, P-R interval of 0.22 sec, and many ventricular premature contractions.

The patient was treated with a maintenance dose of 0.33 mg of Digilanid daily but developed severe peripheral edema and many fine rales at both lung bases. On January 9, 1956, he was given 0.66 mg Digilanid orally. On Jan. 10, a rapid rhythm was noted but an electrocardiogram was not taken. On January 11, the electrocardiogram showed bidirectional tachy-

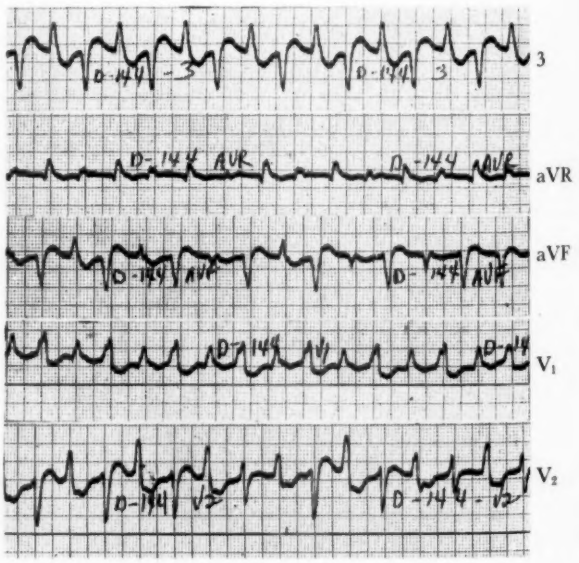

Fig. 5. Case 2. Bidirectional tachycardia.

cardia with short runs of auricular fibrillation (Fig. 5). Sixty meq of potassium chloride in 1,500 cc of 5 per cent glucose in water were given intravenously with no effect on the cardiac rhythm; 10 cc of 25 per cent magnesium sulfate were then given slowly intravenously and the rhythm abruptly changed to auricular fibrillation. Fifteen minutes later the bidirectional tachycardia returned and a second infusion of 10 cc of 25 per cent magnesium sulfate again changed the rhythm to auricular fibrillation. Bidirectional tachycardia returned after 30 minutes. A solution of 20 cc of 25 per cent magnesium sulfate in 500 cc of 5 per cent glucose in water was then given by intravenous infusion, but the bidirectional tachycardia continued. Quinidine 0.4 g every three hours was then administered and following the third dose, auricular fibrillation was again present.

The patient was then placed on a maintenance dose of 0.2 g quinidine and auricular fibrillation continued. The patient, however, did poorly and died on January 16, 1957. Postmortem examination revealed the left ventricle to be markedly hypertrophied and the heart weighed 680 g. Old anterolateral and posterior myocardial infarctions were present. The kidneys showed advanced arteriolar nephrosclerosis and focal chronic pyelonephritis.

Discussion

Although auricular fibrillation was the basic rhythm present prior to the onset of bidirectional tachycardia in case 1 and following its termination, P waves could be definitely seen during the paroxysm, although visible only in lead V_3. The rate was generally regular with minor variations and the QRS complexes were separated by approximately 0.34 second without alternating diastolic lengths. The QRS duration of both complexes was 0.08–0.10 second and one of the complexes resembled some of the ventricular premature contractions previously present, but were shorter in duration and of lower voltage. Neither type of QRS complex resembled the one present before the onset of the bidirectional tachycardia. Although the Valsalva maneuver produced no changes, the application of right-sided carotid sinus pressure caused an equal slowing of both types of complexes. However, the alternating nature of the QRS configurations remained. The tachycardia gradually returned to its original rate. This sequence of events was repeated several times. During the administration of EDTA the rhythm abruptly changed to auricular fibrillation with ventricular premature contractions, similar to that present prior to the onset of bidirectional tachycardia.

The rhythm prior to the onset of bidirectional tachycardia in case 2 was also auricular fibrillation with ventricular premature contractions. No P waves were seen during the paroxysm of bidirectional tachycardia. The interval between successive QRS complexes was about 0.39 second with little or no variation in the diastolic length between the complexes of alternating configurations. The duration of both types of QRS complexes was 0.12 sec. Neither carotid sinus pressure nor potassium administration affected the arrhythmia. On two occasions, however, magnesium sulfate administered intravenously caused temporary cessation of bidirectional tachycardia with the return of auricular fibrillation. Quinidine was then administered and this may have been responsible for permanently abolishing the bidirectional tachycardia.

Case 1 is particularly notable for the presence of P waves, which has not previously been reported to our knowledge. The atrial rate was regular and atrial impulses may have been initiating the ventricular complexes which followed a P-R interval of 0.08 sec. Since the P waves were visible only in lead V_3, the interval may be deceptively short because the initial portion of the P wave may have been isoelectric in this lead. Consideration must also be given to the possibility that the atria and ventricles were beating independently, although at somewhat similar rates. In this type of arrhythmia where a double tachycardia is present, the QRS complexes may be either of nodal or ventricular origin. The occurrence of fusion beats could then explain some of the variations in the QRS configuration which are occasionally observed.

Effect of Vagal Stimulation: The effect of vagal stimulation by either carotid sinus pressure or Valsalva maneuver has been reported to cause cessation of either one or both types of the complexes present.[1,2,7,14] In case 1, however, carotid sinus pressure caused a definite slowing of identical degree of both types of QRS complexes. This result further supports the evidence for the supraventricular nature of the site of the impulse formation in this case. It is, however, most suggestive of impulse formation in

or near the S-A node, since this is not the type of response that would be expected in either atrial or nodal tachycardia. As is the case with atrial tachycardia with block,[15] which is frequently associated with digitalis intoxication, we may be confronted in this instance with a rhythm which is a separate entity despite similarities to several other supraventricular arrhythmias.

Effect of Electrolyte Disturbances: The modifying effect of various electrolytes on the action of digitalis on cardiac muscle has been well established. Potassium depletion predisposes to digitalis intoxication,[16] while the administration of potassium is frequently associated with reversal of toxicity due to digitalis.[17,18] Conversely, calcium administration enhances the toxic effects of digitalis,[19,20] and the administration of calcium salts is known to be hazardous in digitalized patients.[21]

The antagonism between the effects of potassium and calcium on myocardial excitability has been demonstrated in hyperkalemic dogs in whom acute lowering of the serum calcium precipitated fatal potassium intoxication.[22] The administration of calcium to patients with acute renal failure has proved efficacious in the management of hyperkalemia.[23,24] The interrelationships between these two cations on cardiac contraction per se has been studied and the degree of contraction of the frog ventricle at a given concentration of potassium is determined by the level of calcium.[25] Since calcium influences the stability of polarized cell membranes the extent and duration of potassium exchange across the myocardial cell membrane is modified by the calcium concentration.

Lowering of Serum Calcium with EDTA: Acute lowering of the serum calcium has recently been shown to prevent or abolish the manifestations of digitalis intoxication in animals.[22] The salutory effect was prompt, and reversal of the digitalis intoxication occurred in all instances. Gubner and Kallman[26] reported three clinical cases in which arrhythmias due to digitalis intoxication were terminated by lowering the serum calcium with the infusion of sodium EDTA. Six hundred milligrams of disodium EDTA were given intravenously with 5 per cent glucose in water. Subsequent reports have confirmed the beneficial effect of EDTA in arrhythmias due to digitalis intoxication.[27] The results are somewhat nonspecific, however, since ventricular premature contractions unrelated to digitalis intoxication occasionally may be abolished.[28]

The intravenous infusion of EDTA in case 1 rapidly terminated the bidirectional tachycardia and resulted in the reappearance of auricular fibrillation. Ethylenediamine tetraacetic acid is a powerful chelating agent which quickly lowers serum calcium.[29] The calcium chelate formed is a stable nonionized complex at physiologic pH. The ability of EDTA to combine with calcium has been previously utilized in efforts to lower abnormally elevated calcium levels[30] and to dissolve corneal opacities,[31] and in attempting to eliminate renal calculi.[32,33] Serious renal toxicity and bleeding tendencies due to prolonged prothrombin time occurred with large doses of EDTA,[34] but single intravenous infusions of 3 g of sodium Versenate are considered to be safe and free from serious side effects.[35]

Effect of Magnesium: Although recent studies have emphasized the interrelationships between calcium, potassium, and digitalis, other electrolytes such as sodium and magnesium may play a significant role in the complex mechanisms involved. Enselberg[36] has reported the beneficial effects of magnesium sulfate on digitalis intoxication, and both bidirectional tachycardia and atrial tachycardia with block[15] due to digitalis intoxication have responded to the administration of magnesium sulfate. In case 2, the administration of magnesium sulfate terminated the bidirectional tachycardia on two occasions when intravenous potassium had produced no response. However, the transient effect which usually occurs when magnesium sulfate is administered greatly impairs its clinical effectiveness.

Summary of Treatment: Because of the high mortality associated with bidirectional tachycardia, its occurrence calls for prompt and effective therapeutic measures. If digitalis has been given it should be discontinued temporarily. It is apparent that no single treatment is efficacious in all instances. Both carotid sinus pressure and magnesium sulfate are of

limited value because of the transient nature of the response elicited by them. Potassium administration does not always terminate the arrhythmia, as illustrated by case 2. Quinidine may be of value in some cases. The successful use of EDTA, which was administered in case 1, has not been previously reported in the management of this arrhythmia and should be considered as one of the first agents to be used because of its apparent safety and the promptness of the response. Although preliminary studies indicate that the response of digitalis-induced arrhythmias to EDTA may be short-lived in some instances,[28] further clinical trial is suggested.

Summary

Two cases of bidirectional tachycardia are presented, and the etiologic and diagnostic considerations are reviewed.

In one of the cases, lowering of the serum calcium with EDTA therapy resulted in the prompt disappearance of the arrhythmia. This case differs from previously reported ones, since P waves were present during the episode and carotid sinus pressure resulted in slight slowing of both types of complexes.

The second case responded to magnesium sulfate on several occasions but the effect was transient.

Since digitalis may be implicated in the development of this arrhythmia, further clinical trial with EDTA is suggested in cases of bidirectional tachycardia.

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Reviews

Mechanism of Origin of Ectopic Beats

A Hypothesis, with Special Reference to Extrasystoles*

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A STUDY of the mode of origin of ectopic beats is of great interest, not only in view of its obvious clinical importance, but also in a wider physiologic context. The mechanism of impulse formation and conduction can be investigated in some detail, suitable methods being readily available which range from conventional electrocardiography to measurement of ionic movements and recording of intracellular potentials.

The more recent intracellular recording of potentials has shown that in cells of the myocardium proper, for example of a papillary muscle, the membrane potential remains constant during diastole. In cells of a pacemaker, on the other hand, a slow depolarization was found during diastole; when this attains a certain degree and the membrane is thus depolarized to the threshold level, a propagated response is precipitated. This distinctive process in pacemakers had been found already before the advent of intracellular recording[7,17] ("pre-potentials" of Arvanitaki[3]). The underlying mechanism is not yet known.

Normally, the center with the highest rate of impulse formation situated in the sinoatrial node dominates the heart, because a propagated wave of excitation thus precipitated depolarizes all other potential centers. In certain circumstances, however, there may be temporary A-V rhythm in healthy subjects if the rate of impulse formation in the A-V node exceeds that in the sinus node. This has been observed if changes in the tone of the autonomic nervous system result in a greater inhibition of impulse formation in the S-A than in the A-V node (due, for example, to change of position or associated with respiratory arrhythmia). Similarly, temporary coronary sinus rhythm is not uncommon in healthy subjects. Parasystole is another arrhythmia due to automaticity of a center other than the S-A node; this will be discussed.

MECHANISMS OF EXTRASYSTOLES

Definition: For reasons given in detail elsewhere, we have suggested separating from arrhythmias due to automaticity the clinically common arrhythmia which is due (with very rare exceptions) to ectopic beats following the preceding beat at a constant interval, that is, with fixed coupling, and it is this variety which alone we have proposed to term "extrasystoles."[40] It may be said from the start that no one mechanism has been established which would explain all instances of this disturbance of rhythm.

Two Main Theories: There are two main theories about the underlying mechanism; namely, that of a re-entry mechanism and that of an origin of the ectopic impulse in an abnormal focus. Both have one important and, in

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Certain original work described in this review was supported by a grant-in-aid (H-230) from the National Heart Institute, U. S. Public Health Service.

our opinion, unquestionably correct assumption in common: The beat preceding the extrasystole initiates it and is therefore the precipitating beat. It follows that, contrary to the belief held some thirty years ago[50] that extrasystoles are an "active" phenomenon, an extrasystole is a passive phenomenon in the sense that its appearance depends on the preceding initiating beat; it is a "forced contraction," as Lewis once called it.[24]

Re-entry Mechanism

These theories regard disturbances of conduction as the primary factor, the excitation wave of the initiating beat encountering an area of refractory tissue. After the portions of the myocardium surrounding this focal zone are activated, the excitation wave is presumed to reach, from different directions, this area which, meanwhile, had become excitable again; its excitation would thus provide the starting point of a second activation of the heart—the extrasystole.

RETURN EXTRASYSTOLES

On the grounds of experimental observations this explanation is entirely acceptable for one special variety of extrasystoles, the so-called return extrasystoles. These may be initiated either by A-V nodal beats with preceding activation of the ventricles, provided the R-P interval attains or exceeds a certain critical length, or by ventricular extrasystoles with retrograde conduction to the atria.[41] In either case, the excitation wave, after activating the atrium or on its way to do so, returns to activate the ventricle a second time. A longitudinal dissociation of parts of the A-V conducting system was postulated as an explanation.[31] The presence of fibrotic septa in the A-V conduction system suggests the possibility that one portion of this system may conduct to the atria the impulse which is then conducted to the ventricles by a different section. This conception was modified by Decherd and Ruskin[12] in order to explain certain details of their observations. However, apart from the distinctive type of initiating beat, this variety of extrasystoles differs from the common one by the fact that two different parts of the heart are involved.[45] The number of clinical observations where a diagnosis of return extrasystoles is acceptable is small.[40]

EXTRASYSTOLES WITH FIXED COUPLINGS

A similar re-entry mechanism has been assumed to account for the common variety of extrasystoles with fixed coupling. In certain details, the conceptions put forward by different authors vary. Wenckebach and Winterberg[50] postulated a block in a peripheral twig of the conducting system. The portion of the myocardium supplied by this twig is assumed to be activated by adjacent portions, the excitation wave subsequently being conducted with delay in a retrograde direction through the affected twig. By the time the excitation reaches the junction between the affected and unaffected twigs, the latter has regained its excitability and, by conducting the excitation wave a second time, makes possible a re-entry which gives rise to an extrasystole. An essentially similar concept, though varying in detail, has been put forward more recently by Katz and Pick.[22] Ashman and Hull[5] assume the existence of a portion of the myocardium with a prolonged refractory phase, through which the excitation is conducted with delay; by the time it reaches the adjacent portions of the myocardium they have become excitable again and from there the heart is stimulated a second time.

Inasmuch as these theories are based on experimental observations, Schmitt and Erlanger's investigations[42] on strips of ventricular muscle of the turtle are mainly quoted in support. In these experiments, conduction in the strips was depressed by various means. These authors found that, in some experiments, an impulse precipitated at one end of the strip, having traversed the strip in one direction, returned to excite a second time that part of the strip from which it had originated. They explained these observations by assuming a functional longitudinal dissociation in the muscle strip over a certain distance; the impulse is assumed to be conducted in one direction through one section of the strip, though with delay, and to return in the opposite direction to its point of origin through a different part of the strip through which conduction in the original direction was blocked (unidirectional block).

There are several objections against applying these observations to the explanation of the common variety of extrasystoles with fixed coupling. In the first place, conditions in excised muscle strips of turtle hearts in which conduction was experimentally impaired differ so widely from those in the whole heart in situ, with its highly specialized conducting system, that observations made in the former cannot unreservedly be applied to the latter. But quite apart from this, the results themselves of these experiments have more recently been explained differently, and we believe more correctly, in accordance with observations on nerves and hearts obtained with modern methods. Arvanitaki found in the nerve and heart that an impulse passing through an altered area initiated there oscillatory after-potentials which could give rise to the emission of further impulses ("pseudo-reflex").[4] Reflected excitation waves were seen in heart muscle strips and explained by after-potentials by Bozler and Segers.[7,43]* According to all these authors an excitation wave reaching an altered area initiates there another impulse formation Disturbances of conduction need not be postulated to explain these phenomena. The part played by after-potentials will be further discussed below. It will therefore be seen that Schmitt and Erlanger's observations can be interpreted in a way that they actually support the theory of ectopic impulse formation as the mechanism underlying the origin of extrasystoles.

OBJECTIONS TO RE-ENTRY THEORY

If thus any experimental basis of the theory of re-entry is very slender, there are serious general objections against it.

The length of coupling of most extrasystoles has been a stumbling block to its acceptance for a long time. Persistent couplings of 0.3 second are by no means rare; in fact, the usual range is between 0.3 and 0.6 second. Considering the high velocity of conduction in the myocardium and particularly in the specialized conduction system, a theory primarily based on a prolongation of the refractory period and delay in conduction could hardly explain this arrhythmia as a persistent feature. As far as atrial extrasystoles are concerned, as long ago as 1925 Lewis[24] pointed out that there is no path of sufficient length in the atria for a circulating wave to move during the interval of coupling.

The principle of re-entry implies that the zone of impaired conduction is accessible from only one direction, where the excitation, once initiated, has to pass at another place into the myocardium which had become excitable again. These conditions could only be visualized in certain exceptional circumstances, being due to local variations in the resting membrane potential and the excitability in the border zone.[46] Many patients exhibit the same type of extrasystoles for many years. Disturbances of conduction, as the underlying mechanism, seem most unlikely to account for creating such conditions persistently over long periods.

Another objection is provided by the lengths of coupling with increasing heart rate: If a re-entry mechanism, that is, primarily a conduction disturbance, were to account for such extrasystoles, lengthening of the coupling with increasing rates should be expected, since with higher rates impairment of conduction would become more pronounced. This is not the case; actually, the coupling remains unchanged or tends to become shorter.[23]

A further point against this theory is the effect of warming and cooling of the site of origin of experimentally produced extrasystoles, discussed below.

Ectopic Impulse Formation

The essential concept of this theory is the assumption that the extrasystole is generated in an ectopic focus where local changes of electrical potential become temporarily suprathreshold and precipitate a propagated excitation. This concept, which is in accordance with and supported by numerous observations on cardiac and nervous tissue, is based on two main interrelated factors: (1) a temporary rise in excitability consequent upon a preceding propagated wave of excitation and (2) local changes of electrical potential in an ectopic focus.

SUPERNORMAL PHASE

Regarding a temporary increase in excitability

* Bethe found in the muscle of *Medusa* "reflected contractions" which he compared with extrasystoles with fixed coupling.[6]

consequent upon a conducted impulse, the supernormal phase comes first to mind. Such a temporary overswing of the recovery curve, during which phase stimuli, which would be subliminal at any other time, evoke a response, was first demonstrated in nerve by Adrian and Lucas[2] and in the frog heart in certain experimental circumstances (for example, perfusion with a relatively acid fluid) by Adrian[1] in 1920. Though there is still controversy over whether the supernormal phase can constantly be found in normal hearts,[8,11,49] its presence in certain experimental conditions and clinical cases is beyond doubt.[40] Such increased excitability after a propagated action potential is associated with a negative after-potential occurring toward the end of the phase of repolarization. In the experiments of Brooks *et al.*[8] on the heart of dogs, the supernormal phase was found to last 50–200 milliseconds.

The close relationship between increased excitability, negative after-potential, and arrhythmias was demonstrated in the isolated frog heart by Segers.[44] In nerves, during the supernormal phase the local response to subliminal stimulation was shown to be larger, could be produced by shocks which were weaker, and turned into a propagated spike at a potential which was lower than during the resting period.[19] Furthermore, it has been demonstrated in various tissues, including the heart, that artificial stimuli near the threshold intensity produce a disproportionately great change in membrane potential; also that, in the heart, the threshold potential for natural excitation corresponds approximately to that for an artificial stimulus during the supernormal phase of excitability.[49] The tendency of extrasystoles to occur at the time of the U wave of the initiating beat, which is regarded as an expression of the negative after-potential, also points to this as a possible mechanism of origin.[23]

This seems a plausible explanation for extrasystoles occurring immediately after myocardial infarction, trauma, during cardiac catheterization, and possibly with certain infections (e.g., diphtheria). In all these conditions, injury currents have to be assumed and it has been shown that an electrical field between depolarized and intact tissue precipitates extrasystoles.[15]

OBJECTIONS TO SUPERNORMAL-PHASE EXPLANATION

However, while this explanation may apply to extrasystoles occurring in the above-mentioned conditions, we do not believe that it is acceptable for the common variety of extrasystoles with fixed coupling, frequently observed in otherwise healthy hearts. In the first place, in normal hearts a supernormal phase has not been demonstrated constantly and, where it was found, the increase in excitability was comparatively small and of limited duration. Furthermore, the application of a substance which more than any other prolongs the negative after-potential, namely veratrine,[18] though readily precipitating ectopic beats, does not by itself give rise to extrasystoles with fixed coupling in the dog[37] and rarely does so in man. Lastly, the length of coupling of most extrasystoles is such that increase in excitability after a conducted impulse would have to last much longer than supernormality can be assumed to do. However, there are, in fact, observations of such prolonged increase in excitability far exceeding the duration of the supernormal phase. Of these, the Wedensky effect is the most important one in the present context.

Wedensky Effect: In the sciatic-gastrocnemius preparation of frogs, Wedensky[48] found that subthreshold faradic stimulation of the nerve was followed by a tetanus after one maximal induction shock was applied proximally to the site of (continuing) subthreshold stimulation. It was then also established by Mogendowitsch[25] that the application of a moistened crystal of NaCl between the muscle and the site of stimulation (induction shocks) also precipitated the "Wedensky effect;" the one conducted impulse so lowered the threshold of excitability that, subsequently, the formerly subthreshold stimulation by the NaCl crystal (or the faradic subthreshold stimulation in Wedensky's original experiments) became suprathreshold. In nerves, this "Wedensky effect" lasts far longer than the supernormal phase (more than 0.2 second compared with a few hundredths of a second). It is therefore either a different phenomenon or due to successive stimuli falling within the supernormal phases of the preceding ones.

The presence of the "Wedensky effect" in the heart was confirmed by Goldenberg and Rothberger in excised Purkinje fibers of dogs.[16] It may be the operative mechanism to account for the occurrence of extrasystoles with fixed coupling, and of ectopic tachycardias with fixed coupling of the first ectopic beat, following topical application of NaCl to the cardiac surface of the dog.[26] Some observations on ectopic tachycardias in man have been similarly interpreted.[45] The "Wedensky effect" thus represents a long-lasting change of excitability following a propagated impulse.

LOCAL CHANGES OF POTENTIALS AND AFTER-POTENTIALS

It was mentioned above that local, nonpropagated "pacemaker" potentials consist normally in a slow depolarization; apart from the sinus venosus of the frog heart, they have been recorded in Purkinje fibers. In certain abnormal conditions such local potentials may become oscillatory. These have been demonstrated in various organs, including the heart.[3,7] Similar considerations apply to negative after-potentials following a propagated impulse. In the giant axon of the squid and the heart of the snail, Arvanitaki[3] showed that, under the influence of calcium deficiency, near-threshold stimulation readily induced oscillatory local potentials which periodically precipitated propagated spikes. Rapid multifocal pacemaker activity associated with an increase in the rate of slow diastolic depolarization, due to calcium deficiency, has been demonstrated in Purkinje fibers of the dog.[21]

Effect of Environmental Factors: The influence of environmental factors on after-potentials has been demonstrated in a variety of conditions. The effect of calcium deficiency has already been referred to. Another example is stretching which was found by Scherf, Scharf, and Goklen[39] to initiate and increase the rate of atrial arrhythmias and to initiate arrhythmias elicited by aconitine. By means of intracellular recording of potentials, Dudel and Trautwein[13] showed that stretching of a papillary muscle of the cat's heart produced a marked negative after-potential; and that of Purkinje fibers of dogs elicited shortened excitations in the relative refractory period and spontaneous depolarizations in an ectopic pacemaker which resulted in propagated excitations, culminating in long-lasting pacemaker activity of the center with a high rate. It has also been demonstrated[47] that, in the spontaneously beating Purkinje fiber of dogs, during repolarization one or more depolarizations occur in a variety of experimental conditions, e.g., O_2 deficiency, CO_2 excess, fatigue, digitalis intoxication, veratrine. If such secondary depolarization results in a fully developed action potential, it produces a second excitation which, being consistently conducted with normal velocity, follows the preceding beat with constant coupling. If the secondary depolarization is abortive, it will either die out or be conducted with delay in the vicinity of its focus of origin, velocity of conduction increasing with increasing distance from the focus. These differences therefore provide a basis for the understanding of constant coupling, of differences of coupling in different cases, and of variations of coupling within a certain range.

Oscillatory after-potentials, periodically giving rise to the emission of propagated impulses, would also account for one peculiar variety of ectopic beats, namely those occurring in groups of two or more in succession, such groups being separated by longer intervals. This type of ectopic arrhythmia is uncommon clinically, but not rare in experimental animals.[38] A re-entry mechanism cannot be responsible because of the duration of the pauses between the groups.

Effect of Warming and Cooling: An important argument in favor of a focal origin and against a re-entry mechanism of extrasystoles with fixed coupling is the effect of warming and cooling the focus from which extrasystoles or allied ectopic arrhythmias were produced by the topical application of various substances.[32,34] Irrespective of the compound thus employed—aconitine, NaCl, sodium oxalate and citrate, barium chloride, digitalis—warming of the focus increased the number of ectopic beats or even resulted in an ectopic tachycardia, whereas cooling abolished the arrhythmia. More important still: When extrasystoles with fixed coupling, elicited by one of the above-mentioned substances, had subsided, they reappeared

when the site of application of the substance was warmed. These effects were reproducible at will. Were such arrhythmias due to a re-entry mechanism, warming, which improves conduction and shortens the refractory phase, should not only not increase the rate and number of ectopic beats but should also abolish them. If, on the other hand, an ectopic focal origin is assumed, the increase in rate of de- and repolarization induced by raising the temperature would readily explain these observations, a marked effect of temperature changes on pacemaker depolarization having been demonstrated.[36,49]

EFFECT OF DRUGS IN PRODUCTION OF EXTRASYSTOLES

A great variety of substances, when topically applied to the cardiac surface, may produce extrasystoles and ectopic arrhythmias, originating at the site of application. Such arrhythmias vary in several respects, depending on the substance used. Thus, aconitine extrasystoles are usually transformed into flutter and fibrillation within a few seconds. Barium-induced ectopic beats occur at irregular intervals, whereas those produced by sodium appear at regular intervals and with fixed coupling. The latter applies also to extrasystoles elicited by the topical application of digitalis, though they appear only after a long latent period, which is shorter if strophanthin is used.[33,35]

These differences, as well as the observation that dilute acids do not produce ectopic arrhythmias at all, suggest that the arrhythmic properties of the above-mentioned compounds are specific for each, and not due to one common underlying factor, such as an effect on conduction or an osmotic action. The observation that under the influence of digitalis and strophanthin extrasystoles appear in single Purkinje fibers also supports the view that they originate in a center as opposed to being due to a re-entry mechanism.[10,14]

Furthermore, when extrasystoles with fixed coupling were produced in dogs by the systemic administration of aconitine, every additional ectopic beat, wherever and however artificially elicited, was found to be followed by an extrasystole of the same shape as those following the beats of the dominant rhythm (status bigeminosus).[29] This observation can be readily understood if a focal origin is assumed. With the heart in this sensitized condition, any excitation wave arriving at the ectopic focus from whatever direction triggers off the same type of extrasystole; this could hardly be visualized were the extrasystoles due to a re-entry mechaism resulting from delay of conduction in one direction.

The constancy or near-constancy of coupling despite variations in rate of the dominant rhythm is also understandable on the assumption of a focal origin of the extrasystole. For example, Bozler[7] found that acetylcholine and adrenaline did not alter the frequency of the local oscillatory changes of potential, while reducing and increasing, respectively, their magnitude. Thus it is understandable that single extrasystoles occurring at longer intervals have the same coupling whenever they appear.

In order to explain why so often only one extrasystole occurs it should be remembered that in the ectopic center the negative after-potential (associated with increased excitability) is often followed by a positive after-potential (hyperpolarization of the membrane) with subnormal excitability.

That many substances, among them compounds in everyday clinical use, may elicit as well as suppress ectopic arrhythmias has been known for a long time, but only of late has the mechanism underlying such dual action begun to be understood owing to recent electrophysiological work.[9,46,49] Its result is entirely consistent with the view of a focal origin of such arrhythmias. As far as acetylcholine is concerned, the inhibitory effect has often been shown. Its stimulating effect has recently attracted increasing attention, largely due to the work of Burn and his collaborators.[9] Conversely, stimulation of the sympathetic nerves and epinephrine may, according to the circumstances, initiate or abolish extrasystolic arrhythmias.

Digitalis and Extrasystoles: Digitalis is another substance well known for suppressing as well as precipitating extrasystoles. Extrasystoles could be elicited by application of strophanthin or

digitalis to any spot area of the surface of the dog's ventricle.[33] This result already favored the assumption of an ectopic impulse formation as the responsible mechanism. Though the underlying mechanism has not yet been clarified, it seems worth noting that in the papillary muscle of the cat the duration of the plateau and action potential *increases* at the beginning of strophanthin intoxication, but subsequently *decreases* as intoxication proceeds. Similar opposite effects during successive stages of increasing intoxication were found regarding the membrane resistance.[14] It seems to us likely that these changes are associated with variations in ionic permeability and thus have a bearing on the dual effect of digitalis glucosides on arrhythmias, and also on the antiarrhythmic effect of potassium in ectopic digitalis arrhythmias.

A discussion of ectopic arrhythmias due to digitalis provides a convenient opportunity of re-emphasizing that extrasystoles cannot be attributed to increased excitability of the heart, for digitalis reduces excitability. The conditions for such arrhythmias to appear are more complex, as is also demonstrated by the fact that in normal subjects even very large doses, though producing profound disorders of conduction, do not give rise to ectopic arrhythmias.[40]

Quinidine and Procaine Amide: That the commonly used antiarrhythmic drugs, like quinidine and procaine amide, may give rise to ectopic arrhythmias as well as suppress them is an established fact, but the underlying mechanism is not known. Vaughan Williams,[51] studying the effect of quinidine on isolated rabbit atria, pointed out that the great reduction in the rate of rise of the action potential produced by quinidine, in even small concentrations, necessitates a higher degree of repolarization after a conducted impulse for a propagated action potential to become possible. Basing his explanation on observations on the relation between rate of rise of an action potential and the membrane potential from which the action potential develops, he thus reconciled the paradox that this drug lowers the frequency at which propagated impulses can arise, although the absolute refractory period remained unchanged or was even shortened by this drug. Here again, the primary effect was shown to be on excitation, effects on conduction being secondary to it.

EXTRASYSTOLES IN HEART BLOCK

In complete A-V block, extrasystoles with fixed coupling are quite common. Regarding their underlying mechanism, two considerations seem to apply: First, a mode of origin akin to "Wedensky facilitation," that is, an increase in excitability beyond a block induced by various means, as discovered by Wedensky in nerve in 1903, and further investigated by more modern methods by Lorente de No and by Hodgkin.[20] However, to our knowledge, this phenomenon has not yet been demonstrated in cardiac muscle. Oscillatory local potentials have been observed in connection with this phenomenon in nerve.[28] Second, the same type of lesion which causes the block is likely to create conditions precipitating extrasystoles, for example O_2 deficiency (see above). In this variety of extrasystoles, too, we do not see any reason to attribute the extrasystoles to a re-entry mechanism.

Automatic Ectopic Rhythms

As distinct from extrasystoles in the strict sense of the term as employed by us, that is, ectopic beats with fixed coupling to the preceding beat (except for the very rare sinus extrasystoles which are not ectopic), there are various ectopic rhythms which are due to the independent activity of an ectopic pacemaker. The example *par excellence* is, of course, the ventricular rhythm in complete A-V block. More pertinent in the present context is parasystole, due to the coexistence of sinus rhythm with an automatic idioventricular rhythm; more pertinent because it is often considered identical in its mode of origin with that of extrasystoles, a view which we consider erroneous.

Parasystole: In the uncomplicated case of parasystole, beats due to the ectopic pacemaker become manifest whenever they fall outside the refractory period of the sinus beats, and vice versa. This results in an arrhythmia exhibiting two characteristic and diagnostic features: (1) the ectopic beats occur with varying coupling to the preceding beat; and (2) at such times when a sinus *and* an ectopic ventricular

beat are due, the shape in the electrocardiogram of the complexes of such beats show a combination of the features of the two, i.e. combination, summation, or fusion beats. Furthermore, within certain limits, all interectopic intervals are multiples of the underlying ectopic cycle length* and stand in simple mathematic relations to one another. With extrasystoles with fixed couplings, the last mentioned relations also obtain, but are only the result of the fixed coupling.

In parasystole, the idioventricular beats are due to the activity of an automatic center entirely independent of the preceding beat whereas, as emphasized above, in extrasystoles, the ectopic beats not only cannot be ascribed to increased automaticity of the ectopic center but often occur in conditions of generally depressed automaticity, such as under the influence of digitalis. While the analysis of cases of parasystole leaves no doubt about the underlying mechanism, its explanation encounters one essential difficulty which has not yet been satisfactorily resolved: It has to be assumed that the ectopic center is depolarized by its own automatic impulses, whereas it is not depolarized by the conducted impulses of the other (S-A) center. The nature of this mechanism protecting the ectopic center from the sinus beats is still obscure. We believe that such a protection is related to the ratio of *strength of impulse: excitability*, whereas we do not consider the assumption of an area of refractory tissue surrounding the center ("protection block") as an acceptable explanation.

Apart from physiologic considerations, the separation of parasystole from extrasystoles with fixed coupling is also justified on clinical grounds: Whereas extrasystoles are often found in otherwise healthy hearts, this is the rare exception in parasystole. A very small number of cases has been reported in which parasystole changed into extrasystoles with fixed coupling. Such observations demonstrate that occasionally the same ectopic center which produces automatic beats can also produce true extrasystoles dependent on the initiating beat; they do not prove identity of these two arrhythmias.[40]

* Ectopic cycle length = interval between two successive ectopic beats not separated by any sinus beat.

Dissociation with interference is an arrhythmia in which a faster A-V rhythm coexists with a slower S-A rhythm, whereby the A-V impulses are prevented from reaching the atria by a unidirectional block in the direction A-V node to atria, whereas the orthograde conduction remains intact. This results in those S-A beats which fall outside the refractory phase of the A-V node and ventricles activating the ventricles and interrupting as premature beats the otherwise regular sequence of A-V rhythm.

Ectopic Beats and Specialized Tissue

The question of whether ectopic beats, and extrasystoles in particular, arise only in specialized tissue or whether they may also originate in the ordinary myocardium has been controversial for a considerable time. We have reviewed the relevant literature elsewhere[40] and concluded that in certain experimental conditions ectopic impulse formation is possible in any part of the heart; whether the presence of specialized tissue is necessary remained undecided. The observation that substances like aconitine, when topically applied subepicardially to the left atrial appendage which, in the human heart and that of the dog, according to all competent observers,[27] is devoid of specific fibers, precipitate ectopic arrhythmias originating in the focus of application, suggests that ectopic arrhythmias may originate in ordinary atrial myocardium.

Regarding the presence of specific fibers in other parts of the heart, opinions of authorities vary. Competent observers are in agreement, however, that it is difficult and sometimes impossible to determine microscopically whether an individual fiber is an ordinary myocardial one or belongs to the specialized conducting system.

Conclusions

While we believe that the theory of ectopic focal impulse formation explains the common variety of extrasystoles with fixed coupling far more satisfactorily than that of a re-entry mechanism, we would like to point out that this is not more than a working hypothesis. Furthermore, the two theories have various essential conceptions in common: The dependence of the extrasystole upon the preceding, that is,

initiating beat; and the origin in a small area. Regarding disturbances of conduction, we are aware that they may play a part, but we lay the emphasis on the origin of the impulse in an ectopic focus as the primary factor, whereas any conduction disturbances, if and when present, are secondary and depend on the time of occurrence, and height and rate of rise of the action potential of the extrasystole.

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The Mechanism of Atrial Fibrillation and Flutter*

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THE MAJOR THEORIES to date concerning atrial fibrillation and flutter are (1) a single ectopic atrial focus, (2) multiple ectopic foci, and (3) the circus movement. That a relationship existed between ectopic beats, paroxysmal tachycardia, and atrial flutter and fibrillation was first advanced by Hering in 1900 (quoted by Hecht[1]). Englemann was the first to state the theory of multiple ectopic foci.[3] For many years this theory was championed by Lewis[1] and it was also favored by the Viennese school.

Another school of thought was initiated by Lewis. He thought that a circus movement was the basis of atrial fibrillation and flutter. This theory was the result of some brilliant experimentation, although some estimates were used in view of the limitations of the experiments. The theory that a single ectopic atrial focus, with rapid-frequency discharge, was the trigger for the mechanism of atrial fibrillation and flutter was postulated by Rothberger and Winterberg.[3] Scherf was also impressed by this theory as a result of his first experiments with aconite.[3]

Prinzmetal,[2] in his animal experiments, produced atrial fibrillation and flutter by using electrical stimulation and aconite. He studied the heart in man during commissurotomy and in experimental mammals, using cinematographic and electrocardiographic methods. In view of his studies he accepted the single focus theory.

Just about the time that the circus movement theory was in question, due to the work of Prinzmetal, Rosenbleuth's experiments[1] tended to strengthen Lewis' concept. By crushing a muscular bridge between the venae cavae in a mammalian heart, Rosenbleuth and Garcia Ramos created an obstacle around which the impulse circulated perpetually and atrial flutter was maintained.[1]

Katz and Pick[3] felt that atrial fibrillation and flutter could not be accounted for by any single theory. They stated that a single ectopic impulse, occurring during a nonrefractory period of the heart cycle, might start atrial fibrillation and flutter. When multiple re-entry developed, the arrhythmias were perpetuated and the pattern of the re-entry determined the type of arrhythmia.

With the possible exception of those arrhythmias produced by vagal stimulation and acetylcholine, stimuli used to cause the arrhythmias in mammals have no relationship to those that cause arrhythmias in the human being. Also, the experimental mammals were not suffering from heart disease.

In the human being atrial fibrillation and flutter occur more frequently in mitral stenosis than in any other cardiac condition. It is estimated that two-thirds of all patients with mitral stenosis suffer from atrial fibrillation. The next most common cause of atrial fibrillation and flutter is thyrotoxicosis. A review of the physiologic studies in mitral stenosis and thyrotoxicosis may give the clue to the possible cause of these arrhythmias.

ELECTROPHYSIOLOGY OF NORMAL CARDIAC CELL

The study of intracellular electrophysiology has contributed greatly to the knowledge of cardiac cell function.[5] With the Ling-Gerard

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microelectrode the resting and action potential of the cardiac cell can be measured. When two electrodes are placed on the outside of a resting single cardiac fiber, no potential develops. However, when one of the electrodes is introduced *into* the cardiac fiber, a transmembrane potential of 100 mv is registered (Fig. 1).

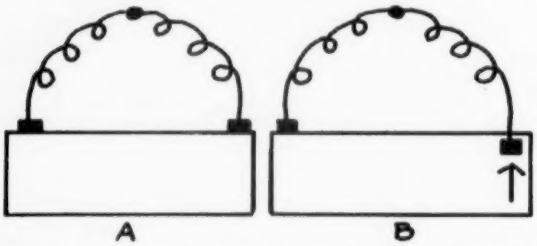

Fig. 1. Cardiac cell resting potential. (A) Electrodes on surface of resting cardiac fiber. (B) Electrode inside resting cardiac fiber. Arrow indicates electrical flow.

The origin of the cardiac cell resting potential is due to the ratio of K^+ *inside*:K^+ *outside*:: *30:1*. During the resting period, the cell membrane is permeable to K^+ but very little to Na^+. The potassium ions move across the membrane because of their gradient, creating a K^+ potential with outward current flow. When the cell membrane becomes charged, the flow of potassium stops. The K^+ *inside*:K^+ *outside* ratio is the most important factor in creating and stabilizing the cell resting potential. During diastole the resting potential of the cardiac cell is stable.

When a resting cell is stimulated, there is increased membrane permeability to Na^+. The movement of Na^+ inside the cell creates a sodium potential, causing the action potential. The various phases of the action potential are represented graphically in Figure 2. The increase of Na^+ inside the cell makes the cell more positive inside than outside. The action potential phenomenon is transient and reverses itself in the resting stage.

Characteristics of Normal Pacemaker Cell: The cardiac pacemaker cell varies from nonpacemaker cells in that it has a lower resting potential and a slow depolarization phase. The pacemaker cell begins to depolarize as soon as the terminal rapid repolarization phase reaches the resting level of the cell. The cell stimulates itself, causing a slow depolarization phase. When it reaches the threshold potential, which is the point of cell polarization reversal, it suddenly fires off (Fig. 3). The characteristics of a pacemaker cell may be assumed by other cardiac cells under certain conditions.[4]

For normal heart excitation it is necessary to have normal cell depolarization and repolarization. The cell membrane must be stable during diastole, the pacemaker cell must have a lower resting potential, and the threshold potential has to be constant. Variations in any of these factors in the cardiac or pacemaker cells may predispose to arrhythmias. The resting potential of the pacemaker cell and the slow depolarization phase can be affected greatly by vagus or sympathetic stimulation (Fig. 4). This was demonstrated by Weidmann on the frog heart.

Effect of Vagal and Sympathetic Stimulation: A

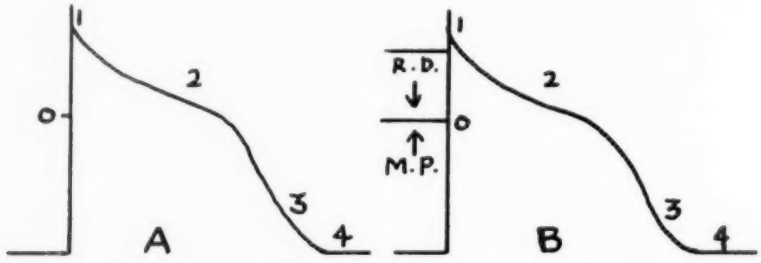

Fig. 2. Action potential, various phases. (A) Rapid depolarization (overshoot) begins at point *0*, which represents the level of membrane potential at which there is a reversal of polarization and the net membrane current becomes inward. First phase, rapid repolarization, *1*. Slow repolarization (plateau), *2*. Second phase, rapid repolarization (terminal), *3*. Diastolic portion, *4*. (B) MP, membrane potential and RD, rapid depolarization (overshoot) equal the depolarization phase of the action potential. Action potential repolarization lasts from *1* to *4*. Arrows indicate direction of electrical flow.

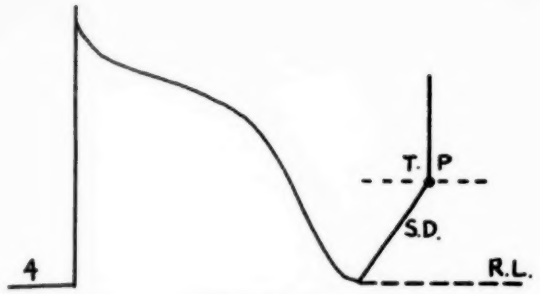

Fig. 3. Pacemaker cell. *S.D.* represents slope of slow depolarization. *T.P.* represents the threshold potential. *4* is the diastolic portion or the resting level of the cell, *R.L.*

short stimulus of the vagus decreases the slope of the slow depolarization phase, requiring more time to reach the firing level, and the heart is slowed. Sympathetic stimulation has the opposite effect. However, prolonged vagus stimulation depresses the slope of the resting potential of the pacemaker cell to the point where hyperpolarization is present. This prevents the pacemaker from firing.[5] This experiment shows that prolonged vagal stimulation can eliminate the S-A node as a pacemaker and allow the lower centers to take over.

Physiologic Basis for Atrial Fibrillation in Mitral Stenosis

In moderately severe mitral stenosis the atrium is dilated and the muscle fibers are stretched. There are varying degrees of anoxia present. Electrolyte changes may easily occur. The anoxia and the stretch of the muscle fibers which augments the anoxia shortens the repolarization phase and reduces the resting potential of the cardiac cell, which in turn increases the automaticity in previously quiescent areas, creating potential pacemakers.[6] The vagus stimulation is strong and prolonged.[7] With suppression of the S-A node and shortening of the refractory period of the cardiac cell, the start and perpetuation of atrial fibrillation and flutter may occur.

In moderately severe cases of mitral stenosis, the excessive vagus stimulation and the factors that lower the membrane resting potential of the cardiac cell are the prerequisites to fibrillation. It would seem that atrial flutter is a transitional stage to atrial fibrillation in which the resting potential of the cardiac cell is more stable than in fibrillation. Quinidine, by stabilizing the resting potential of the cardiac cell and by inhibiting the action of the vagus, can restore atrial fibrillation and flutter to normal rhythm.

Physiologic Basis of Atrial Flutter and Fibrillation in Thyrotoxicosis

In thyrotoxicosis the stimuli of sympathetic and parasympathetic systems are increased. There is great predominance of the sympathetic stimuli. Since atrial fibrillation is often associated with strong vagal stimulation, it is difficult to explain the frequent occurrence of atrial fibrillation with thyrotoxicosis. In mammalian experimentation in which thyrotoxicosis was caused and then acetylcholine injected, atrial fibrillation developed.[8] In patients with thyrotoxicosis the arrhythmias can also be produced by injecting acetylmethylcholine.[9]

Excitation of the sympathetic fibers causes shortening of the refractory period of the cardiac cell. It also increases the automaticity of all normally nonpacemaker tissue, at times to the point of production of ectopic beats.[10] Acetylcholine acts like the vagus. It helps produce

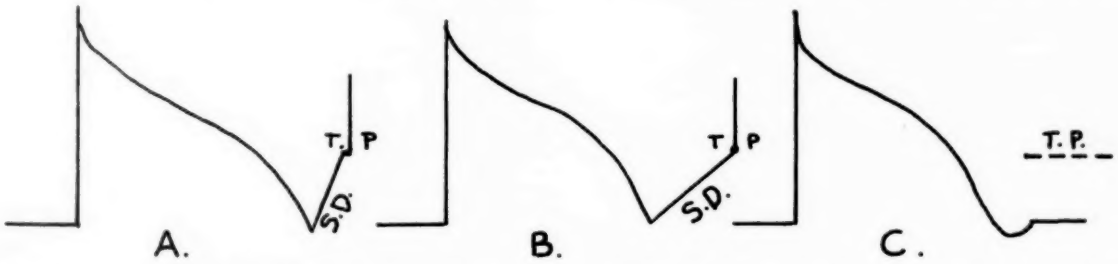

Fig. 4. Effect of nerve stimulation on pacemaker cell. (A) Effect of sympathetic stimulation. Slope increased; heart rate increased. (B) Effect of vagus stimulation. Slope decreased; heart slowed. (C) Prolonged vagus stimulation. S.D. slope unable to reach T.P.

atrial fibrillation and flutter in thyrotoxicosis by depressing the S-A node and further shortening the refractory period of the cardiac cell.

Comments

The electrical and mechanical manifestations in atrial fibrillation differ completely from those in any other atrial arrhythmia. The conduction and contraction are totally disorganized, as if numerous pacemakers were controlling different groups of atrial muscle. The spontaneous firing of the ectopic pacemakers can be brought about in any cardiac cell by depressing the stability of the resting potential of the membrane. In atrial fibrillation there is no coordination between the different muscle groups, for some may be in systole at the same time that others are in diastole. Uncoordinated depolarization waves spreading from ectopic pacemakers meet areas that are still refractory and are deflected. It is possible that patterns of circus movement may form, but only secondary to irregular pathways of heart depolarization.

Atrial flutter is probably caused by a rapid-firing ectopic focus. It clearly represents a series of rapid and regular atrial contractions that are actively effective. Esophageal or endocardial leads taken during atrial flutter differ little from the atrial complexes obtained in the same area during normal sinus rhythm. In normal rhythm, in paroxysmal tachycardia, and in flutter, the P configuration difference in the ECG is not as marked as one would expect. Atrial flutter is unstable and slight increases in atrial rate cause impure flutter which is an intermediate stage between flutter and fibrillation.

Apparently in the majority of cases the production of atrial fibrillation and flutter depends on strong and prolonged vagus stimulation of the heart, causing suppression of the S-A node and shortening of the refractory period of the cardiac cell.

When the resting potential of the cardiac cell becomes unstable, ectopic pacemakers are created and the stage is set for the initiation of atrial fibrillation and flutter.

Summary

Atrial fibrillation and flutter are caused by strong, prolonged vagus stimulation and by factors that disturb the stability of the resting potential of the cardiac cell.

Anoxia, stretch of the cardiac fiber, or electrolyte changes tend to disturb the resting potential of the cardiac cell, creating pacemakers.

Vagus stimulation suppresses the S-A node allowing the created pacemakers to take over. When the refractory period is shortened, the ectopic pacemaker has more possibility of becoming effective.

In mitral stenosis there is prolonged vagus stimulation and the resting potential of the cardiac cell changes. These factors produce atrial fibrillation and flutter.

In thyrotoxicosis, sympathetic stimulation shortens the refractory period of the cardiac cell. The sympathetic stimulation also causes the resting potential of the cell to become unstable, thus producing ectopic pacemakers.

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Mechanisms Determining Reciprocal Rhythm Initiated by Ventricular Premature Systoles

Multiple Pathways of Conduction*

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WHEN AN impulse originating in the A-V node or an ectopic ventricular focus is conducted to the atria, it may occasionally turn back somewhere in its course to activate the ventricles again. This activation is called reciprocating rhythm,[23] reciprocal rhythm,[7] reciprocal beating,[3,17] or return extrasystole.[27] Reciprocal rhythm has been described more often as initiated by A-V nodal systoles. The subject has recently been reviewed.[28] Reciprocal rhythm initiated by ventricular premature systoles has been recorded infrequently.[10,13,15,17,18,20,22,25,28,31]

The recognition that retrograde conduction to the atria from ventricular premature systoles is common in man[4,15] stimulated this study. The quantitative analysis of considerable data in four cases brings out a number of mechanisms which determine reciprocal rhythm initiated by ventricular premature systoles and throws additional light on mechanisms involved in cardiac conduction in general. Tracings were recorded simultaneously by esophageal and standard leads.[14] This method made possible observations and measurements not otherwise obtainable. Indeed, in two of the cases (cases 3 and 4) the existence of reciprocal rhythm would not otherwise be recognized and in a third (case 2) the existence is more firmly established.

The peak of the esophageal P wave (onset of "intrinsic deflection") is used as a more precise reference for measurement than the onset of P. In a previous study[15] concerned with absolute values of the ventriculoatrial (V-A) conduction time this reference in the retrograde P was designated I′ to distinguish the V-A times obtained in this way from others reported in the literature measured from onset of QRS to onset of P. In the present study the designation P′ is used for the same reference point. Electrocardiograms were recorded at a

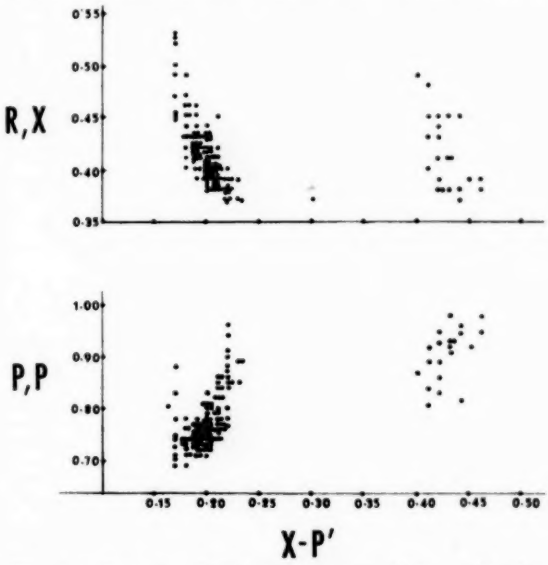

Fig. 1. Case 1. Relations between V-A conduction time (X-P′) and the P,P cycle preceding the ventricular premature systole (lower) and between X-P′ and the interval from the preceding ventricular systole to the ventricular premature systole (R,X) (upper). Two separate orders of magnitude of V-A conduction time give evidence of two pathways for V-A conduction. Time = seconds. (Reproduced from *Circulation* 3: 738, 1951, by permission of Grune & Stratton, publishers.)

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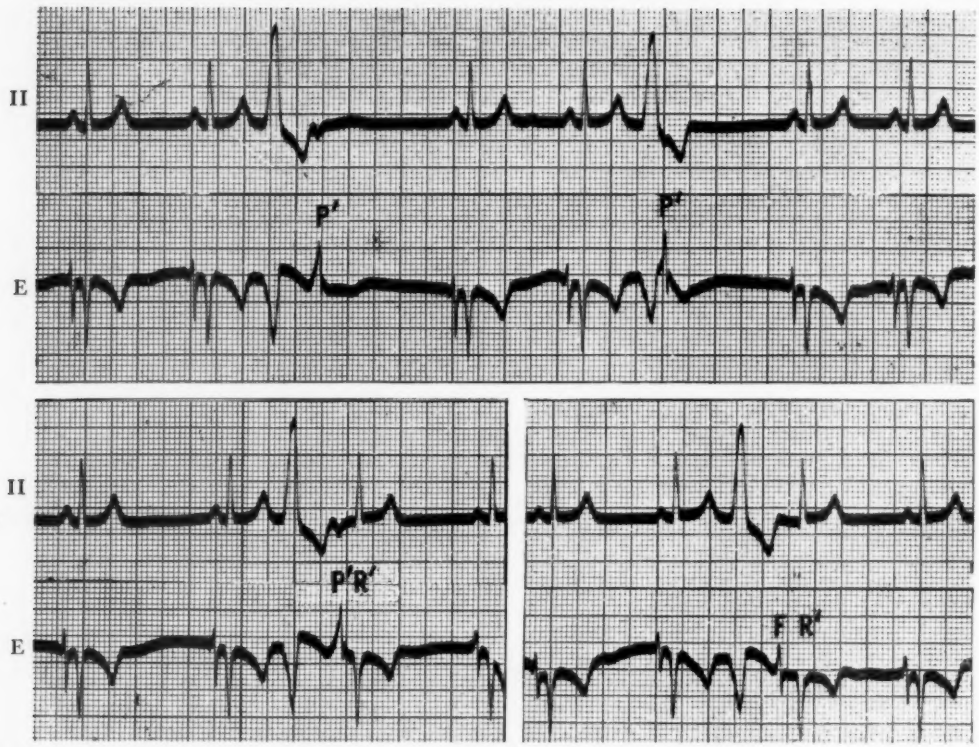

Fig. 2. Case 1. Simultaneous lead II and esophageal lead (E), electrode 37.5 cm from nares. First ventricular premature systole, upper strip, followed by retrograde conduction to the atria (P′), slow V-A conduction. Second ventricular premature systole, upper strip, followed by retrograde conduction to the atria (P′), fast V-A conduction. Lower left, slow V-A conduction and reciprocal beat (R′). Lower right, slow V-A conduction, fusion atrial systole (F), and reciprocal beat (R′). Two orders of magnitude of V-A conduction; evidence of two pathways. Data in Figure 1 and text.

paper speed of 25 mm/sec; the smallest time division in the illustrations is 0.04 second.

The measurements and relationships described in the four cases may be followed more readily if these facts or hypotheses are appreciated: (1) Reciprocal rhythm depends on prolonged V-A conduction time.[28] (2) Clinical evidence[15] and, recently, experimental evidence[24] for multiple conduction pathways have been presented. (3) The refractoriness of the A-V node depends on the duration of the immediately preceding cardiac cycle.[21] (4) V-A conduction time from ventricular premature systoles depends on the time of occurrence of the premature systole in the cardiac cycle.[15] (5) Atrial and ventricular systoles not manifestly conducted across the A-V node may influence subsequent conduction.[16]

Fuller discussion of these tenets follows the presentation of the data. Preliminary mention is made here to indicate why data were accumulated and are presented which pertain to V-A conduction time, to the duration of the cardiac cycle immediately preceding the premature systole, and to the interval between the premature systole and the preceding systole. The finding in the data of what the author considers further evidence for multiple conduction pathways led in particular to a detailed analysis of this phenomenon in relation to reciprocal rhythm.

Observations

Case 1. *Two pathways of V-A conduction; reciprocal rhythm after delayed conduction; effect of duration of cardiac cycle.*

Numerous ventricular premature systoles occurred in a young man admitted to the hospital for tonsillectomy. There was no evidence of heart disease.

The reciprocal rhythm in this case was illustrated in a study of retrograde (V-A) conduc-

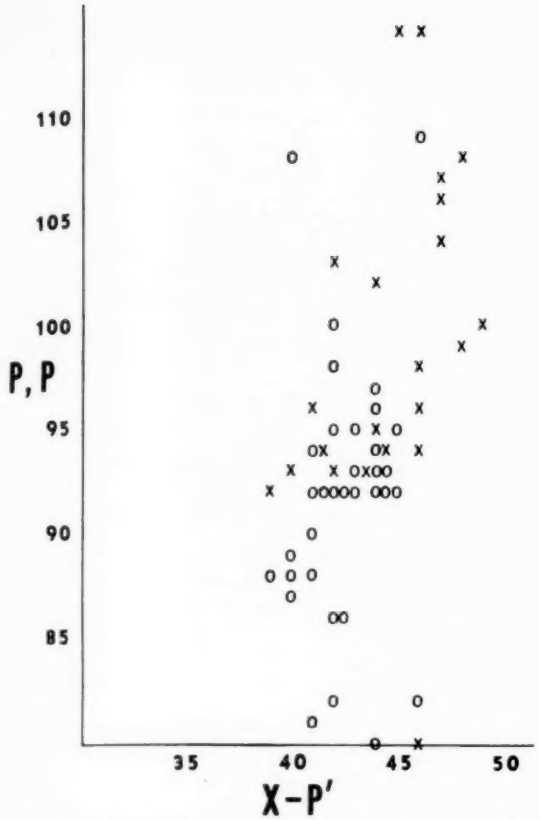

Fig. 3. Case 1. Among the long V-A conduction times, relations among the P,P cycle preceding the ventricular premature systole, retrograde conduction time (X-P′) and reciprocal beats (X). O = no reciprocal beats. Time = hundredths of a second.

tion[15] but not analyzed at that time. It was shown that the V-A conduction times fell into two distinct orders of magnitude (Fig. 1) and it was hypothesized that this represented two pathways. The slow retrograde conduction is illustrated in Figure 2, upper left, and the rapid conduction, upper right. Reciprocal beats are illustrated in the lower strip of Figure 2. The one on the left clearly follows an inverted P wave in lead II and an esophageal P wave different in contour from the sinus P wave. The reciprocal beat on the right, however, follows an esophageal P intermediate in contour between a sinus P and a retrograde P, probably a fusion of the two, and no P is discernible in lead II.

There were 217 ventricular premature systoles with V-A conduction times of 0.16 to 0.24 sec, and none of these was followed by reciprocal rhythm. There were 70 ventricular premature systoles with V-A conduction times of 0.39 to 0.49 sec, and 26 of these were followed by reciprocal rhythm. These data do not correspond exactly with those of Figure 1, because additional measurements were made from the original tracings for the present study; these confirm the relations of Figure 1. There was sinus arrhythmia, and the slower retrograde conduction was more apt to occur when the ventricular premature systole followed a longer P,P interval (Fig. 1). Within the group of ventricular premature systoles with slow V-A conduction, reciprocal rhythm was more apt to occur when the premature ventricular systole followed a longer P,P interval (Fig. 3). The occurrence of reciprocal rhythm was unrelated to the interval between the ventricular premature systole and the preceding ventricular systole.

There was a distinct tendency for the V-A conduction time from premature systoles to be inversely related to the time from the retrograde P wave to the next QRS produced by reciprocal rhythm (P′-R′), the latter reaching a minimum for the longer V-A times.

CASE 2. *Paroxysmal tachycardia due to reciprocal (circus) rhythm initiated by a ventricular premature systole; two pathways of conduction; reciprocal rhythm after delayed conduction.*

Frequent premature systoles and paroxysms of tachycardia occurred in a 64-year-old woman with anxiety but no evidence of heart disease.

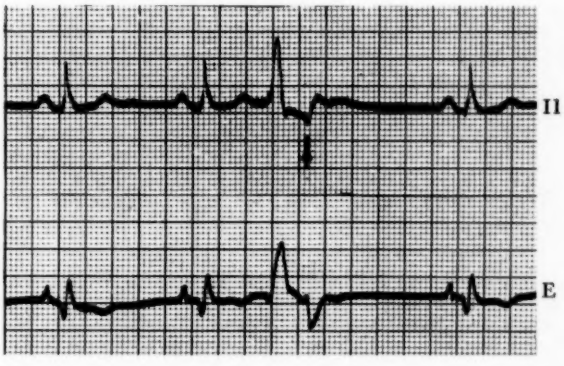

Fig. 4. Case 2. Simultaneous lead II and esophageal lead (E). Retrograde conduction to the atria, short V-A conduction time. Arrow points to inverted (retrograde) P′ in II, confirmed by simultaneous retrograde P′ in E lead.

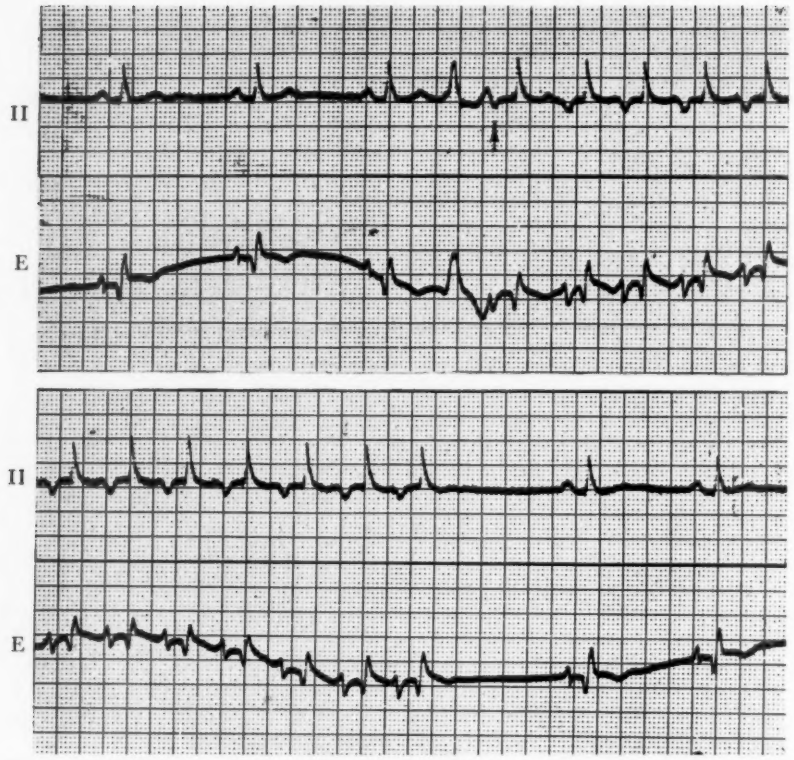

Fig. 5A. Case 2. Simultaneous lead II and esophageal lead (E). Lower strip continuous after the upper strip. Retrograde conduction to the atria, long V-A conduction time, followed by reciprocal rhythm, paroxysmal tachycardia. Arrow points to inverted P′ in II, confirmed by P′ in E lead earlier than expected sinus P. Inverted P′ waves in II after each QRS of the tachycardia except the last. Absence of P in the E lead preceding the ventricular premature systole is proof that the latter is not aberrant conduction after hidden atrial premature systole.

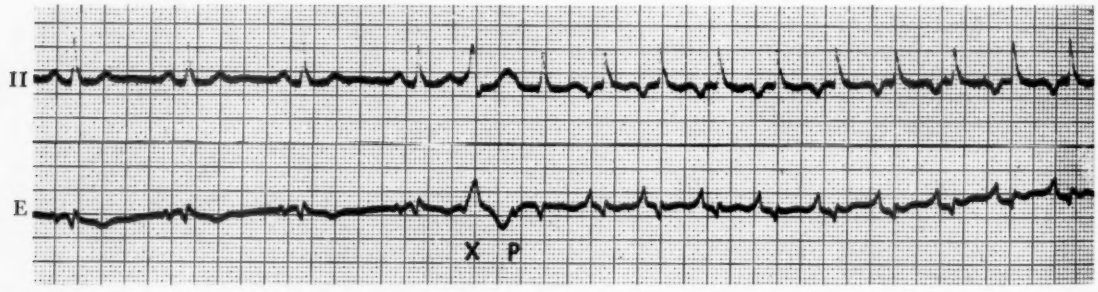

Fig. 5B. Case 2. Simultaneous lead II and esophageal lead (E). Level of esophageal electrode different from Fig. 4, 5A, 5C, 5D. Tachycardia after ventricular premature systole. Atrial systole of sinus origin (P) follows X. If reciprocal rhythm is initiated by X, bypass is below atrium. Possibility that sinus impulse is conducted and followed by reciprocal rhythm and tachycardia, discussed in text.

The premature systoles were from three different foci, and all produced retrograde conduction to the atria, (Figs. 4, 5A, 5C, 5D). The V-A conduction time varied considerably. Sometimes the ventricular premature systole was followed immediately by a sinus P wave rather than a retrograde P wave (Fig. 5B). After some of the slower V-A conduction times and when a sinus P immediately followed the premature systole by a long interval reciprocal rhythm occurred. Instead of a single reciprocal cycle there were paroxysms of tachycardia with inverted P waves in lead II and normal QRS complexes. This happened after ventricular premature systoles from all three foci, a total of 13 times (Figs. 5A, 5B, 5C, 5D, 7).

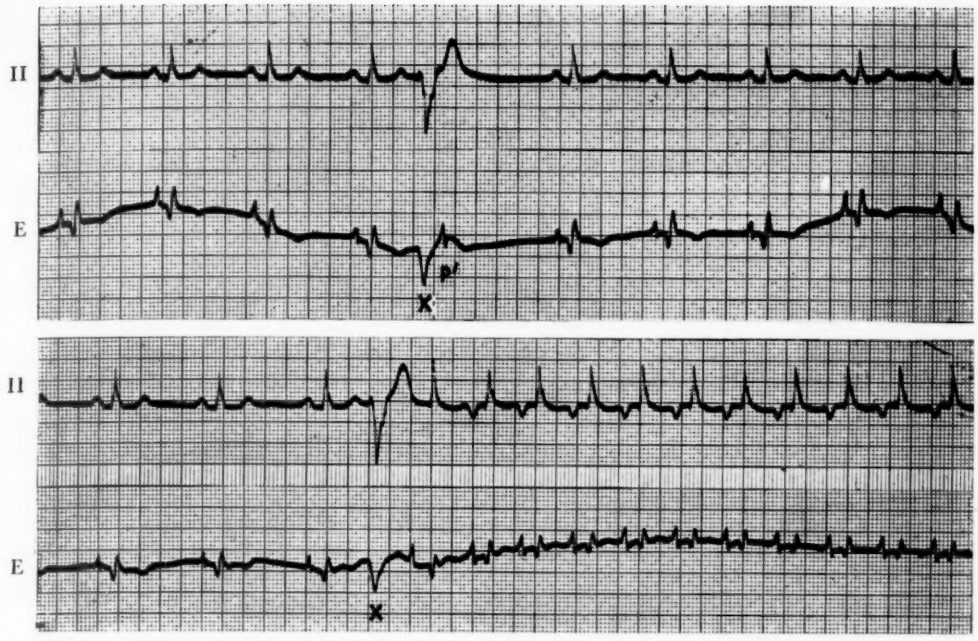

Fig. 5C. Case 2. Simultaneous lead II and esophageal lead (E). Second ectopic ventricular focus. Upper strip, rapid V-A conduction from ventricular premature systole (X-P′), no reciprocal rhythm. Lower strip, X followed by reciprocal rhythm and tachycardia. Superimposition on T complicates interpretation of atrial systole after X; it occurs at time of expected atrial systole of sinus origin, but slight difference in contour suggests possible fusion of retrograde and forward impulses in atria.

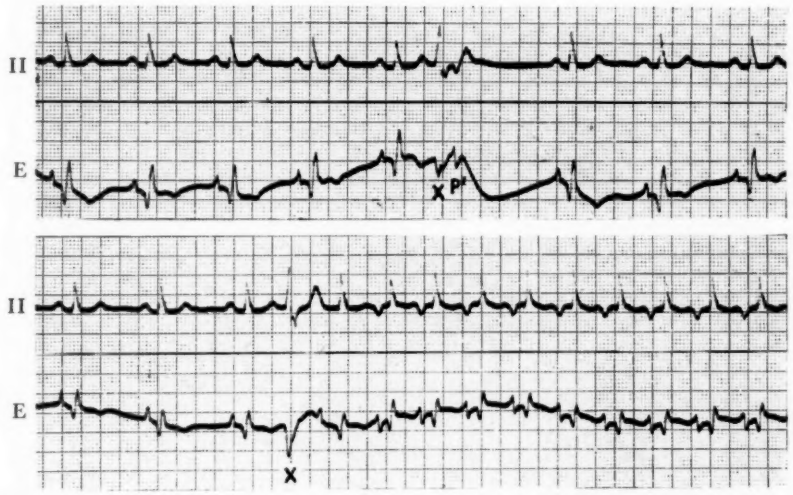

Fig. 5D. Case 2. Simultaneous lead II and esophageal lead (E). Third ectopic ventricular focus. Upper strip, rapid V-A conduction from ventricular premature systole (X-P′), no reciprocal rhythm. Lower strip, X followed by reciprocal rhythm and tachycardia. Superimposition on T complicates interpretation of atrial systole after X; it occurs at time of expected atrial systole of sinus origin, but slight difference in contour suggests possible fusion of retrograde and forward impulses in atria.

In Figure 5A an inverted P′ follows the premature systole in lead II, and this is confirmed by the distinct P′ in the simultaneous esophageal lead, earlier than the expected P of sinus origin.

Figure 6 shows the relations to the P,P cycle immediately preceding the ventricular premature systole and to the interval between the premature systole and the preceding ventricular systole (R,X) of (1) the ventriculoatrial

conduction time from the premature systoles (X-P′) and (2) the interval from the ventricular premature systole to the following sinus P wave when the latter immediately followed the premature systole (X,P). X-P′ times of 0.21 to 0.32 sec were not followed by reciprocal rhythm and tachycardia. One X-P′ of 0.43 sec occurred (Fig. 5A). In a few instances at X,P times of 0.40 to 0.46 sec it was possible that the P following X was due to fusion of retrograde and sinus impulses (Fig. 7). After the X-P′ time of 0.43 sec and after X,P times of 0.41 to 0.54 sec reciprocal rhythm and paroxysmal tachycardia occurred. Sometimes the ventricular ectopic beats occurred during the paroxysms of tachycardia (Fig. 7).

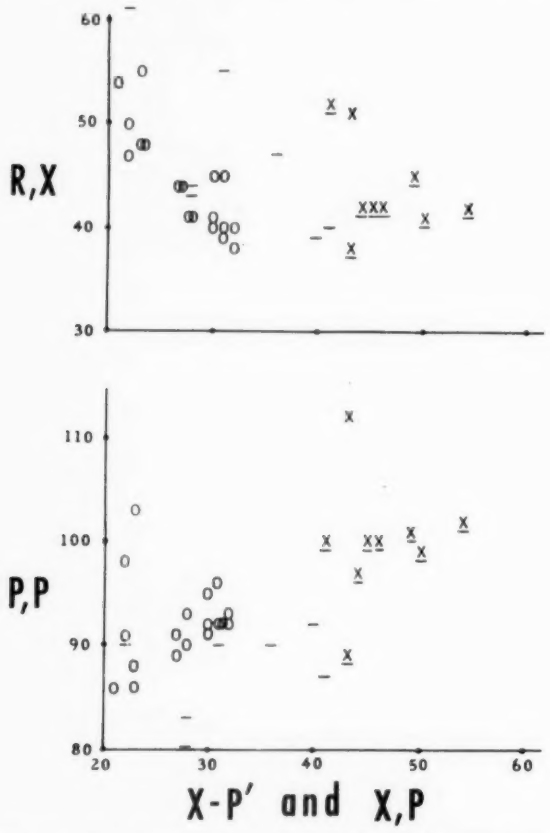

Fig. 6. Case 2. Relations between P,P cycle preceding ventricular premature systole and retrograde (V-A) conduction time (X-P′), or time from ventricular premature systole to sinus P (X,P), lower. Relations between interval from preceding ventricular systole to ventricular premature systole (R,X) and X-P′ or X,P. O = X-P′ not followed by reciprocal rhythm. — = X,P not followed by reciprocal rhythm. X = X-P′ followed by reciprocal rhythm and paroxysmal tachycardia. $\underline{X}$ = X,P followed by reciprocal rhythm and paroxysmal tachycardia. In some instances P of — and $\underline{X}$ possibly due to fusion of retrograde and forward atrial activation.

After premature systoles from a second ventricular ectopic focus (Fig. 5C), there were four instances of X-P′ from 0.24 to 0.25 sec and no reciprocal rhythm. In three instances X-P′ was 0.35, 0.36, and 0.43 sec, and reciprocal rhythm and tachycardia occurred after the X-P′ time of 0.43 sec. A sinus P wave occurred once 0.22 sec and once 0.36 sec after the premature systole not followed by reciprocal rhythm. A fusion (? sinus) P occurred once 0.40 sec and once 0.42 sec after the premature systole followed by reciprocal rhythm and tachycardia (Fig. 5C).

After premature systoles from a third ectopic focus there were 2 X-P′ times of 0.21 sec, not followed by reciprocal rhythm. A sinus P occurred once 0.32 sec after the premature systole not followed by reciprocal rhythm. A fusion (? sinus) P occurred once 0.40 sec after the premature systole followed by reciprocal rhythm and tachycardia (Fig. 5D).

The data were inadequate to test the relation of the V-A conduction time to the interval from the retrograde P to the next QRS produced by reciprocal rhythm.

CASE 3. *Reciprocal rhythm after ventricular premature systoles in succession; reciprocal rhythm after delayed conduction.*

There were numerous ventricular premature systoles from many different foci in a 72-year-old man with arteriosclerotic heart disease and congestive heart failure. Ventricular premature systoles resulted in retrograde conduction to the atria except those which occurred simultaneously with or soon before or after an atrial systole. Frequently two and sometimes three premature systoles occurred in succession, and the V-A conduction time after the last premature systole was longer than after the first (Fig. 8). Sometimes with these longer V-A conduction times there was reciprocal rhythm (Fig. 8).

There was an inverse relationship between the V-A conduction time after a premature systole and the interval since the previous activation of the A-V node. The index for the interval since previous activation of the

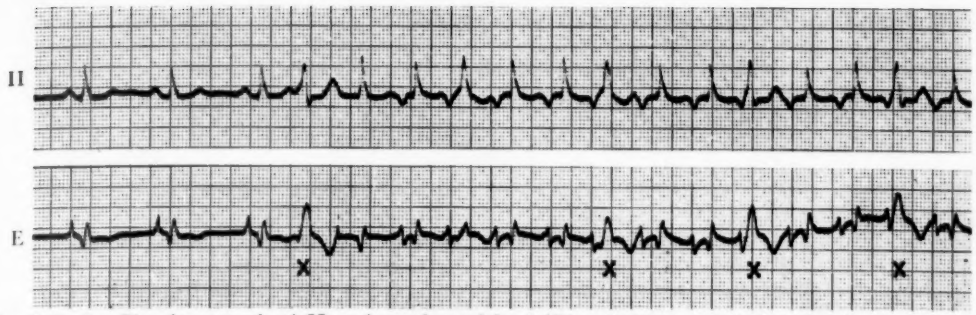

Fig. 7. Case 2. Simultaneous lead II and esophageal lead (E). Ectopic ventricular systoles during tachycardia resembling ventricular premature systole which initiates tachycardia by reciprocal rhythm. The ventricular ectopic beats (X) seem to be from a parasystolic focus. Evidence that this is not a tachycardia due to a repetitive nodal pacemaker. The P following the first ventricular premature systole occurs at the time the sinus P is expected and may possibly be due to fusion of retrograde and forward impulses in the atrium.

A-V node for the first of two or three premature systoles was the time from the onset of P preceding the premature systole to the onset of the premature systole. The same index for the second and third premature systoles of a group was the time from the onset of the premature systole in question to the onset of the preceding premature systole. Two separate orders of magnitude of V-A conduction could not be demonstrated. Reciprocal rhythm occurred with V-A conduction times of 0.34 to 0.43 sec, although many conduction times within this range were not associated with reciprocal rhythm.

There was no relation of reciprocal rhythm to the duration of the previous cardiac cycle which was measured as the preceding P,P for the first of a group of premature systoles, the interval from the preceding P to the preceding premature systole for the second, and the interval between the first and second premature systoles for the third.

In the eleven instances of reciprocal rhythm most of the V-A conduction times fell within such a narrow range that it could not be determined whether the V-A time from premature systoles was inversely related to the interval from the retrograde P to the next QRS produced by reciprocal rhythm.

CASE 4. *Three pathways of V-A conduction; double reciprocal cycles; reciprocal rhythm after delayed conduction; relation of conduction time and reciprocal rhythm to previous atrial and ventricular systoles—concealed conduction.*

This complex arrhythmia occurred in a 64-year-old woman with hypertensive heart disease, diabetes mellitus, and congestive heart failure. The possibility of digitalis toxicity was considered, but the arrhythmia became worse on the administration of potassium chloride, and there was temporary improvement when more digitalis was given. Tracings from this case were used to illustrate the method of simultaneous esophageal and standard leads,[14] but the reciprocal rhythm has not previously been analyzed.

The basic rhythm was A-V dissociation (Fig. 9). Ventricular premature systoles occurred from six different foci. These initiated V-A conduction to the atria (Figs. 10, 11, 15) unless they occurred simultaneously with or soon before or after an atrial systole.

The esophageal P waves due to retrograde conduction differ in contour from the sinus P waves and from P waves due to atrial pre-

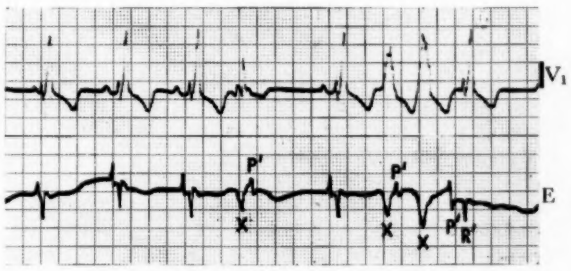

Fig. 8. Case 3. Simultaneous lead V_1 and esophageal lead (E), electrode 35 cm from nares. First and second ventricular premature systoles (X) followed by retrograde conduction, short V-A time (X-P′). Third ventricular premature systole is followed by a longer V-A conduction time (X-P′) and a reciprocal beat (R′). The first P wave of the tracing differs from the next two of the sinus rhythm because it follows the pause after a ventricular premature systole.

TABLE I

Data for Ventricular Premature Systoles with Retrograde (V-A) Conduction and Reciprocal Beats in Case 4

Focus	Group	Number	Figure illustrating	The two systoles preceding X, in sequence	Intervals from preceding ventricular and atrial systole to ventricular premature systole sec × 100		Conduction times sec × 100			
					R,X or X,X	P,X or P′,X, or Px,X	X-P′	P′-R′	R′-P″	P″-R″
X1	a	3	11	R,P	75–83	41–58	45–52	22	—	—
	b	1		X1,P	84	50	47	23	—	—
	c	5	11	X2-P′	76–92	35–54	43–57	21–25	—	—
	d	3	10	R,P	116–134	82–111	31–32	—	—	—
	e	1		X2,P	117	74	32	—	—	—
	f	4	10	X2-P′	96–115	58–76	31–33	—	—	—
	g	2	10	Px-R	74–80	92–104	31–32	—	—	—
	h	1		X2-P′	156	116	51	33	43	23
	i	1		X4-P′	162	115	53	33	45	22
	j	2	11	X5-P′	162–169	113–116	50–52	33–37	43–44	22–23
X2	a	8	12	P,R	90–105	97–113	37–42	—	—	—
	b	10		R-P′	96–136	73–113	36–41	—	—	—
	c	33	11	R,P	90–127	53–110	37–42	—	—	—
	d	3	12	R,P	104–119	88–103	56–58	32–38	41–43	21–22
	e	1		P,R	97	98	60	32	41	22
	f	1		X1,P	106	105	59	31	44	22
X3	a	12		P,R	54–60	66–75	46–52	—	—	—
	b	8	15	P,R	55–61	65–75	64–67	28–32	45–51	20–22
	c	4		R,P	54–57	14–16	65–69	22–24	—	—
X4		2		P,R	58–59	73–74	48–49	—	—	—
X5		4		P,R	56–60	68–74	47–53	—	—	—
X6		1		X3-P′	101	51	53	23	—	—

P = atrial complex of basic sinus rhythm. R = ventricular complex of basic nodal rhythm or result of conduction from atrium. Px = atrial premature systole. X = ventricular premature systole. X1,2,3,4,5,6 = ventricular premature systoles from six different foci. P′ = atrial complex resulting from retrograde (V-A) conduction. R′ = first reciprocal ventricular complex. P″ = atrial complex resulting from retrograde conduction in second reciprocal cycle. R″ = second reciprocal ventricular complex. X,X; P,X etc., = time between the designated complexes which appear in the sequence indicated, but no conduction between them. X-P′; Px-R = time between designated complexes, the latter being conducted from the former. R-P′ = conduction time from A-V node to atrium minus conduction time from A-V node to ventricle. P′-R′; R′-P″; P″-R″ = time between the designated complexes of the reciprocal cycles, but conduction probably by way of bypasses and not necessarily directly between designated complexes (see text and Fig. 14).

X1a and c are illustrated in Figure 11 upper and middle strips, X1j in Figure 11 lower strip, X1d in Figure 10 upper right, X1f in Figure 10 lower left, and X1g in Figure 10 lower right. X2a is illustrated in Figure 12 left, and X2d in Figure 12 right. X3b is illustrated in Figure 15. All events are illustrated by diagrams in Figure 14.

The lettering of the groups in X1,2,3 is for identification only and has no other significance; X1a is not necessarily comparable to X2a, etc.

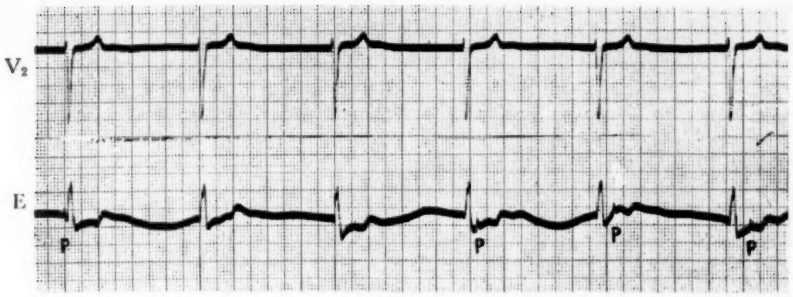

Fig. 9. Case 4. Simultaneous lead V_2 and esophageal lead (E), electrode 39 cm from nares. Basic rhythm, A-V dissociation. P = atrial systoles of sinus origin.

mature systoles (Fig. 10). The time relation of atrial premature systoles to previous QRS complexes is entirely different from that of the retrograde P waves. Slight variations in contour among retrograde P waves are not surprising, because of the possibilities of aberrant conduction, especially when they occur relatively closely together (P′ and P″, Figs. 11, 12, 15). The data for the ventricular premature systoles with conduction to the atria are summarized in Table I.

The dependence of reciprocal rhythm on long V-A conduction times is apparent (Table I and Figs. 10, 11, 12, 15). Sometimes two reciprocal cycles occur (Table I and Figs. 11, 12, 15). The minimum V-A conduction time (X-P′) allowing the first reciprocal beat is 0.43 sec (X1). The failure of reciprocal beats to occur with V-A conduction times of 0.46 to 0.53 sec (X3, X4, X5) is considered in the discussion.

In the data of X2 (Table I; Fig. 12) there are two orders of magnitude of V-A conduction, 0.36 to 0.42 sec and 0.56 to 0.60 sec. The same is true of X3 (Table I) with V-A conduction times of 0.46 to 0.52 sec and 0.64 to 0.69 sec. In each instance, X2 or X3, both orders of magnitude occur at similar intervals between premature systole and preceding ventricular or atrial systole. The possibility that

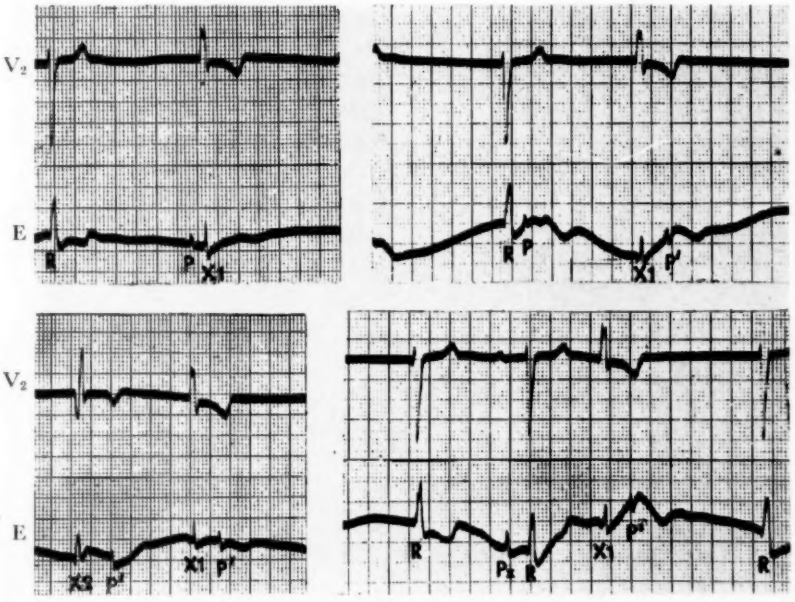

Fig. 10. Case 4. Simultaneous lead V_2 and esophageal lead (E), electrode 39 cm from nares. Upper left, ventricular premature systole (X1) immediately after atrial systole of sinus origin (P), not followed by retrograde conduction to the atria (see Fig. 14, P,X). Other strips show retrograde conduction to atria (X1-P′), short conduction time, no reciprocal beats (see Fig. 14, X1-P′). Data for upper right, Table I, X1d. Data for lower left, Table I, X1f. Data for lower right, Table I, X1g.

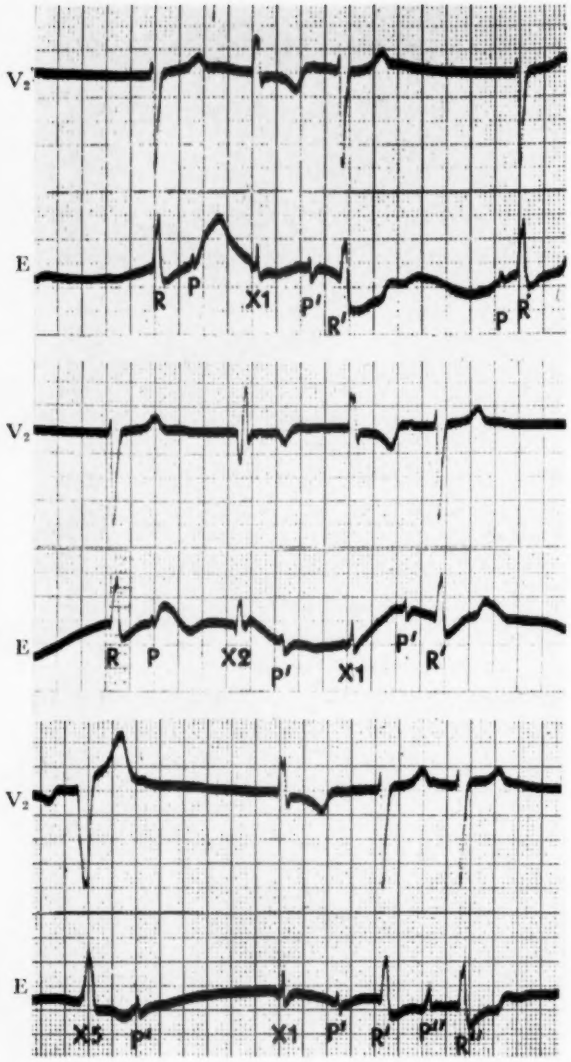

Fig. 11. Case 4. Simultaneous lead V_2 and esophageal lead (E), electrode 39 cm from nares. Upper and middle strips show retrograde conduction to the atria, long V-A conduction time and reciprocal beats (X1-P′-R′) (see Fig. 14, X-P′-R′). Data for upper strip, Table I, X1a. Data for middle strip, Table I, X1c. Lower strip shows retrograde conduction to the atria, long V-A conduction time and two reciprocal cycles (X1-P′-R′-P″-R″) (see Fig. 14, X-P′-R′-P″-R″). Data for lower strip, Table I, X1j.

the two pairs of V-A conduction times after X2 and X3 are actually three different orders of magnitude of conduction time is considered in the discussion.

The distribution of V-A conduction times for X1 is peculiar: X-P′ of 0.43 to 0.57 sec for X1a,b,c; X-P′ of 0.31 to 0.33 sec for X1d,-e,f,g; X-P′ of 0.50 to 0.53 sec for X1h,i,j. The significance of these values is discussed below.

In this case ventricular premature systoles always disturbed the A-V nodal rhythm, in other words discharged the A-V nodal pacemaker, whether they were conducted to the atria or not; there were no interpolated ventricular premature systoles. Reciprocal rhythm always discharged the A-V nodal pacemaker.

The V-A conduction time from premature systoles (X-P′) is not inversely related to the time from the retrograde P to the next QRS produced by reciprocal rhythm (P′-R′, Table I). It is related to the time of occurrence of the preceding atrial systole regardless of whether this is an atrial systole of sinus origin (conducted to the ventricle or not), an atrial premature systole, or an atrial systole resulting from retrograde conduction initiated by a ventricular premature or A-V nodal systole. This is discussed further below.

Discussion

Reciprocal Rhythm and Conduction Time

The dependence of reciprocal rhythm on a sufficiently long V-A conduction time is illustrated in all four cases. The minimum times were 0.39 sec in case 1, 0.40 sec in case 2, 0.34 sec in case 3, and 0.43 sec in case 4. These minimum times are undoubtedly related to the recovery periods of parts of the retrograde and forward paths, probably in or near the A-V node. In most of the reported cases of reciprocal rhythm initiated by A-V nodal systoles, there is evidence that the A-V nodal pacemaker is discharged by the reciprocal rhythm, as in case 4 of this study.[6] The A-V node must, therefore, be common to both pathways and its refractory period a limiting factor in the development of reciprocal rhythm, although Scherf and Shookhoff[27,29] reported "longitudinal dissociation" and interpolated reciprocal beats without discharge of the A-V nodal pacemaker. Where the A-V node is common to both the V-A and return pathways the conduction time from A-V node to the bypass for reciprocal rhythm back to A-V node must be greater than the recovery period of the node for reciprocal rhythm to occur.

The author does not accept the usual ex-

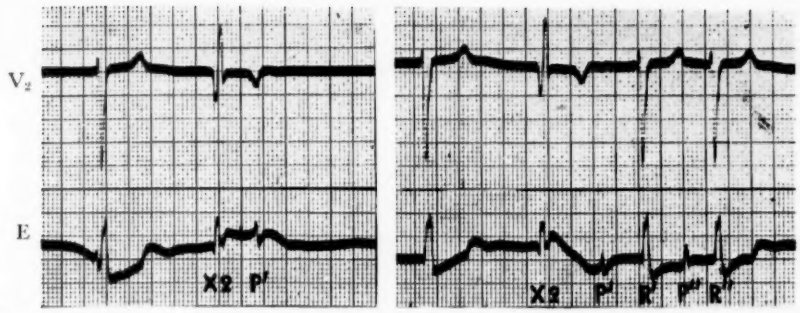

Fig. 12. Case 4. Simultaneous lead V_2 and esophageal lead (E), electrode 39 cm from the nares. Two orders of magnitude of V-A conduction after X2; evidence of two pathways of V-A conduction. Two reciprocal cycles in right strip. Data in Table I, X2a, left strip, X2d, right strip. Sinus P immediately precedes first QRS of left strip. Sinus P falls on first QRS of right strip (as determined by preceding sinus rhythm) and thus not visible. Relations of X2 to previous ventricular and atrial systoles similar in both strips. Relations of X2 to duration of preceding A-V nodal cycle (not shown) also similar. Occurrence of one or the other order of magnitude of V-A conduction "fortuitous."

planation that V-A conduction is necessarily slower than A-V conduction.[15] When longer V-A times occur they may be due (1) to conduction during a relatively refractory period or (2) to failure of response of a fast-conducting pathway in favor of a less refractory, slower-conducting pathway. The latter is discussed in the following section.

MULTIPLE PATHWAYS OF V-A CONDUCTION

Slow and Fast Conduction Times: The evidence for multiple pathways of conduction is the occurrence of separate orders of magnitude of V-A conduction time from ventricular premature systoles in case 1 and case 4 and probably case 2. The duration of the gap between the two orders of magnitude is significantly large compared to the range within each order of magnitude (Fig. 1; X2, X3, Table I; Fig. 12). Either order of magnitude of V-A conduction time may occur sometimes with similar relations of the ventricular premature systole to preceding systoles and after similar durations of preceding cardiac cycles (Fig. 1; X2, X3, Table I; Fig. 12). The durations of the cardiac cycles preceding X2 and X3 are not recorded in Table I; in each of X2 and X3 they were similar for both orders of magnitude of V-A conduction time. The "accidental" appearance of the two orders of magnitude under similar conditions is strong evidence for separate pathways.

In case 2 (Fig. 6) there is a similar tendency to division into two groups of V-A conduction times. Here the longer retrograde conduction times are observed infrequently, and a number of them must be inferred from the fact that reciprocal rhythm occurs when a sinus P follows the premature systole by a long enough interval. The inference is that V-A conduction times longer than X,P would have occurred in these instances if the sinus impulse had not intervened. The retrograde impulse had presumably already reached the bypass for reciprocal rhythm before the sinus impulse could interfere. Another possible interpretation of the tachycardia following X,P is discussed herein.

A closer analysis of the data of Table I suggests the intriguing possibility of a third pathway in case 4. The X-P′ times of X4, X5, and X6, of X1a,b,c,h,i,j, correspond to those of X3a, all these representing one pathway and X3b,c a second pathway. This leaves X1d,e,f,g as a possible third pathway. X2a,b,c corresponds to X1d,e,f,g, and X2d,e,f corresponds to X3a if an impulse from X2 takes several hundredths of a second longer than impulses from other foci to reach the atria. Evidence for the location of X2 is this: In three instances a sinus impulse following X1 was conducted to the ventricles, and the X1,P times were 0.46, 0.47 and 0.49 sec. P followed X2 twice after 0.50 sec and once after 0.49 sec without A-V conduction. One sinus impulse was conducted when X2,P was 0.56 sec. The interpretation is that the A-V node was stimulated sooner after X1 than after X2

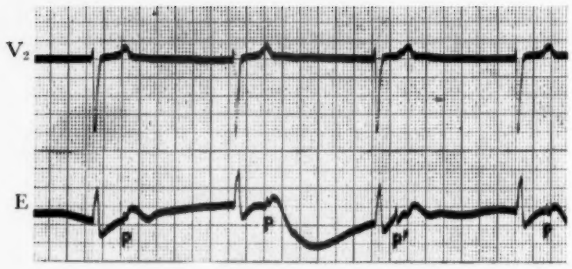

Fig. 13. Case 4. Simultaneous lead V_2 and esophageal lead (E), electrode 39 cm from the nares. Third nodal impulse of basic rhythm conducted back to the atria (P′), (see Fig. 14, R-P′). See text for conditions determining this.

so that it recovered to respond to a sinus impulse after a shorter X,P interval.

Two or more pathways might provide a mechanism for reciprocal rhythm, the impulse going one way along one pathway and returning by the other. Moe and his associates[24] have recently presented evidence for two conduction pathways in the dog and suggest this as a mechanism which might account for reciprocal rhythm. The findings of the present study are a clinical parallel.

Factors of Preceding Cycle Length and Prematurity of Ectopic Systoles: It was shown in case 1 that the fast-conducting pathway is less apt to respond after long cardiac cycles[15] (Fig. 1). If the longest X-P′ and X,P times in case 2 are an index of a slow pathway, then here too failure of response of the faster pathway is more apt to occur after long cardiac cycles and early after previous ventricular systoles (Fig. 6). In case 4 also the faster V-A conduction fails to occur when the premature systole occurs earlier after the preceding ventricular systole (X1a,b,c, X3, X4, X5, Table I). Faster conduction occurs when the premature systole occurs later (X1d,e,f,g, X2a, b,c). These observations may be correlated with recent experimental studies. Mendez *et al.*[21] demonstrated that refractoriness depends on the duration of the immediately preceding cardiac cycle and increases with the duration of the cycle. The observations of Moe *et al.*[24] are consistent with the interpretation that the fast path has a longer refractory period than the slow path; they could demonstrate the slow path by introducing premature systoles very early in the cycle when the fast path failed to respond.

The two factors, preceding cycle length and prematurity of the ectopic systoles, are interrelated for the production of reciprocal rhythm. Long cycles provide the conditions for prolonged refractoriness and recognition of differences between pathways. Ectopic systoles occurring early in the cycle may find the fast path unresponsive, and conduction may occur by way of the slow path. In cases 1 and 2 it is after the longer cycles of the sinus arrhythmia that the slower V-A conduction occurs. In case 4 there are generally abnormally prolonged cycles. In cases 2 and 4 the time of occurrence of the ectopic systole is an additional factor.

There may be other factors which influence the response of the pathways. This is discussed below.

It may be hypothesized, as in the studies of Moe *et al.*,[24] that when the fast pathway is completely refractory the slower pathway serves for V-A conduction, and the fast pathway recovers during the long V-A conduction to serve as the return pathway to the ventricles.

Study of Previously Published Cases of Reciprocal Rhythm for Evidence of Multiple Pathways: A review of the published cases of reciprocal beats reveals that there are usually inadequate data to test the hypothesis of multiple pathways. In some the recorded V-A times are sufficiently far apart to suggest the possibility.[3a,9,11,12,13a]

Decherd and Ruskin[6] described double pathways after A-V nodal systoles—two atrial responses to a single A-V nodal systole, the second atrial response followed by a reciprocal beat. The illustrations of the authors may also possibly be explained by atrial premature systoles after the A-V nodal systoles. According to the hypothesis of multiple pathways as presented here, without further modification, two atrial responses to a single A-V nodal or ventricular systole should not occur. If both paths are responsive, the slow path should be discharged by the impulse conducted along the fast path when the latter reaches their anastomotic juncture (Fig. 14, R-P′, X1-P′). If one path is refractory at the time of stimulation, again two atrial responses should not occur. If the phenomenon described by Decherd and Ruskin

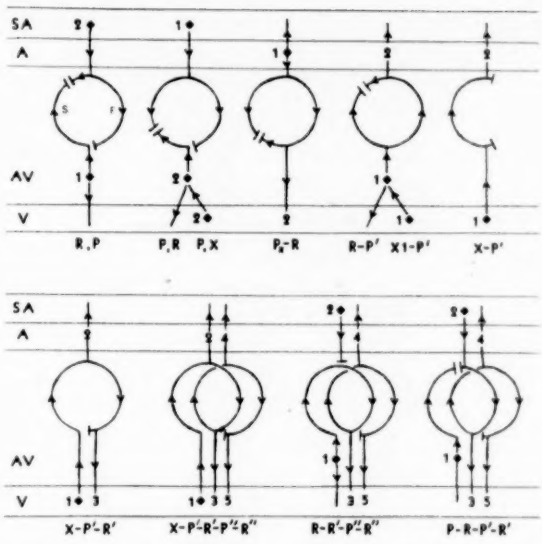

Fig. 14. Case 4. Diagrams of the events in case 4. SA = Sinoatrial node. A = atrium. AV = atrioventricular node. V = ventricle. S = slow pathway and F = fast pathway, designated in one diagram, upper left, for all diagrams. Black diamonds are sites of origins of impulses. Numbers = sequence of activation. Abbreviations under diagrams as in Table I and other figures. Single line at right angles to path of impulse conduction = block during a refractory period. Double line at right angles to path of impulse conduction = interference of conducted impulses from opposite directions. In each of two of the diagrams (P,R P,X and R-P′ X1-P′) two possible events are combined in a single diagram; in both an impulse starts either in A-V node or an ectopic ventricular focus, the remainder of the path toward the atria being the same.

The diagrams are based on the evidence presented in the text for multiple pathways, on the response of F in the V-A direction to an impulse from the A-V node or an ectopic ventricular focus during a limited part of the cycle, but not earlier or later (Table I and text), and on other data.

R,P is illustrated in Figure 9, Figure 10 upper right, Figure 11 upper and middle strips, Figure 13, and Figure 15. This diagram explains also X,P. See legend for P,R P,X.

P,R P,X is illustrated in Figure 10 upper left, Figure 11 upper, and Figure 15. R,P, X,P, P,R, and P,X may be explained by a number of possible combinations of activation of F and S; one is shown. The refractoriness of F for retrograde conduction (following the usual R,R of about 1.50 to 1.57 sec) is guessed from the refractoriness of F in X1h,i,j after X,X1 of 1.56 to 1.69 sec. There is no evidence in data of case 4 to decide responsiveness of F to sinus impulse at this time or degree of penetration if responsive—this part of the diagrams is arbitrarily chosen as one of several possibilities.

Px-R is an atrial premature systole, illustrated in Figure 10 lower right. Atrial nodal impulse activates S and F; F in responsive phase. Interference in S of impulses in opposite directions, both originating in atrium. Px-R time (Fig. 10, lower right) suggests conduction by F. Compare with X1-P′ in Figure 10 whose V-A conduction is also by way of F.

R-P′ X1-P′ is an impulse from A-V node or ventricular ectopic focus conducted to atria. Illustrated in Figure 13 (R-P′), Figure 10 (X1-P′), Figure 11, and 12 (X2-P′). Data for R-P′ in text. Data for X1-P′, Table I, X1d,e,f,g and for X2-P′, Table I, X2a,b,c. A-V nodal or ventricular ectopic focus activates F in responsive phase, conducted by both S and F. Interference in S of impulses in opposite directions, both derived from A-V nodal or ventricular ectopic focus.

X-P′ is an impulse from ventricular ectopic focus conducted to atria. Illustrated in Figure 11 lower (X5-P′). Data in Table I, X3a, X4, X5. Ventricular ectopic impulse reaches F in refractory phase, conducted by S, reaches upper bypass in refractory phase of F.

X-P′-R′ represents retrograde conduction to atria from ventricular ectopic focus and reciprocal beat. Impulse from ventricular ectopic focus reaches F during refractory phase, conducted by S, reaches F at upper bypass during responsive phase, rapid conduction back to ventricle. Second reciprocal cycle does not occur because lower bypass still refractory after recent activation. Illustrated in Figure 11, upper and middle strips. Data in Table I, X1a,b,c, X3c, X6.

X-P′-R′-P″-R″ represents retrograde conduction to atria from ectopic ventricular focus and two reciprocal cycles. Illustrated in Figure 11 lower strip and Figure 15. Data in Table I, X1h,i,j, X2d,e,f, X3b. Impulse from ventricular ectopic focus reaches F during refractory phase, conducted by S, reaches F at upper bypass when F has recovered from refractory phase, reaches lower bypass later than in X-P′-R′ (see text for relations of P′-R′). Lower bypass now recovered from recent activation and responds again to produce second reciprocal cycle. Returning impulse reaches lower bypass sooner than after first cycle. Third cycle does not occur because lower bypass refractory from recent activation.

R-R′-P″-R″ and P-R-P′-R′ represent two possible explanations for the constellation of complexes following the third R in Figure 15. Data in text. The first explanation (R-R′-P″-R″) supposes that the upper bypass is below the atria in A-V node and the mechanism is the same as X-P′-R′-P″-R″ except that there is no retrograde conduction to the atria from the A-V node, the P following the third R of Figure 15 being a sinus P which is blocked because it reaches the upper bypass after the latter has been activated. The second possible explanation (P-R-P′-R′) preferred in the text is that this is a reciprocal cycle following delayed A-V conduction. By this explanation the A-V nodal impulse (giving rise to third R of Fig. 15) is not conducted to the atria because the upper bypass has just been activated by an impulse of sinus origin.

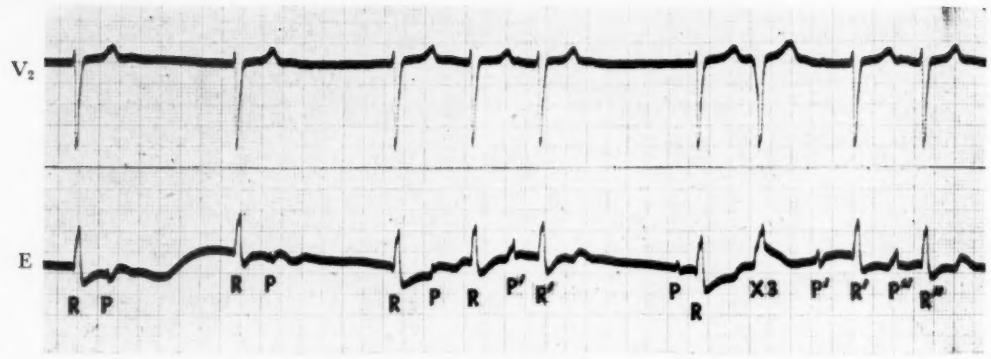

Fig. 15. Case 4. Simultaneous lead V_2 and esophageal lead (E), electrode 39 cm from nares. Two possible interpretations for the constellation of systoles after the third R are shown in the diagrams of Figure 14 (P-R-P′-R′ and R-R′-P″-R″): the first, reciprocal rhythm after delayed A-V conduction and the second, reciprocal rhythm without evidence of retrograde conduction to the atria. Evidence in the text that P-R-P′-R′ more likely. X3-P′-R′-P″-R″ shows two reciprocal cycles, similar to X1-P′-R′-P″-R″ of Figure 11 (see Fig. 14, X-P′-R′-P″-R″). Data for X3-P′-R′-P″-R″ in Table I, X3b.

occurs, it requires special conditions, such as unidirectional block in the slow path, so that it responds in the retrograde direction but not in the forward direction, or refractoriness of the fast-slow juncture at the time of activation by the fast path, with recovery by the time of arrival of the impulse by way of the slow path.

Unidirectional Block: There was no evidence of heart disease in cases 1 and 2, so that the multiple pathways may be a normal mechanism which becomes recognizable under special conditions. It is not necessary in the cases with evidence of multiple pathways to invoke the explanation of unidirectional block. Such block has been demonstrated experimentally[1,30] and reciprocal rhythm in association with it has been observed.[30] Unidirectional block has been used as an explanation for clinical cases of reciprocal beats.[13] The mechanism of multiple pathways hypothesized here is different; the only "block" that occurs is (1) the longer refractory period of the fast pathway and (2) physiologic interference between impulses arriving along a pathway from opposite directions, a consequence of the anastomosis between the slow and fast pathways (Fig. 14).

The demonstration of two pathways does not in itself necessitate the occurrence of reciprocal beats.[15a] The conduction times of both pathways may be too rapid to allow for recovery of the common juncture.

When the V-A conduction times do not fall into separated orders of magnitude, it is not possible to say whether multiple pathways account for the reciprocal rhythm, although multiple paths with overlapping conduction times are possible. In case 3 the mechanism possibly is simply that the second and third of a group of ventricular premature systoles in succession occur earlier in the cardiac cycle and during a more refractory phase. At times there may be slight variations in responsiveness of fibers of what is ordinarily a single pathway, some responding to V-A conduction, others temporarily failing to do so and serving for the return conduction to the reciprocal beat. This would be true temporary unidirectional block. The evidence for the mechanism of multiple pathways has no bearing, of course, on whether or not reciprocal rhythm may also occur through other mechanisms such as temporary or permanent unidirectional block.

FURTHER ANALYSIS OF CASE 4—THE RELATION OF PREVIOUS SYSTOLES TO SELECTION OF PATHWAYS, CONDUCTION TIMES, AND RECIPROCAL RHYTHM—CONCEALED CONDUCTION

The occurrence of fast or slow V-A conduction after ventricular premature systoles in case 4 depends on the interval from the preceding activation of the A-V node (an index of which is R,X or X,X and in one case Px,X (X1g [Table I]). When this interval is 0.54 to 0.92 sec the fast path does not respond (X1a,b,c, X3a,b,c, X4, X5). When it is 0.90 to 1.36 sec the fast path responds (X1d,e,f,g, and X2a,b,c). When it is 1.56 to 1.61 sec the fast path again fails to respond (X1h,i,j).

When V-A conduction is by way of the fast pathway reciprocal rhythm does not occur (X1d,e,f,g and X2a,b,c). The author's interpretation is that in these instances retrograde conduction is by way of both pathways with interference between them (X1-P′, Fig. 14).

When V-A conduction is by way of a slower pathway reciprocal rhythm may or may not occur, depending on the interval from the ventricular systole preceding the ventricular premature systole to the retrograde atrial activation initiated by the premature systole (R,X + X-P′ or X,X + X-P′ [Table I]). When this interval is 1.19 sec (X3c) or greater, reciprocal rhythm occurs. When it is less, 1.00 to 1.11 sec (X3a, X4, X5) reciprocal rhythm does not occur. This interval is probably an index of the recovery time of some part of the fast pathway, activated first by the ventricular systole preceding the ventricular premature systole and activated again by the ventricular premature systole under consideration. The latter activation is by retrograde conduction along the slow pathway to the "upper" slow-fast anastomotic juncture (Fig. 14). A study of the data of Table I shows that the reciprocal rhythm cannot be related to V-A conduction time alone (compare X-P′ of X1a,b,c,h,i,j and X6 with that of X3a, X4 and X5), or to the interval between the preceding ventricular systole and the premature ventricular systole (compare R,X of X3a with that of X3b,c [Table I]).

The interval from ventricular premature systole to preceding atrial systole seems to be related to reciprocal rhythm. The evidence for this involves the analysis of the interval P′-R′ of Table I. The meaning of this interval may be appreciated from Figure 14 as being the difference between the time from the ventricular premature systole to the next ventricular systole produced by reciprocal rhythm (X-R′) and the V-A conduction time (X-P′). For similar retrograde conduction times in X1a,b,c and X1h,i,j the corresponding P′-R′ intervals differ. Also for similar retrograde conduction times in X3b and X3c the corresponding P′-R′ intervals differ. Assuming that the similar X-P′ times mean consistent similar conduction throughout the retrograde pathway, P′-R′ may be briefer because a return pathway is activated earlier, or because a shorter return pathway is activated, or because conduction in the return pathway at the time of activation is faster. Whichever of these occurs, the differences in P′-R′ seem to be related to the time of the preceding atrial systole. When the P,X or P′,X intervals are 0.14 to 0.58 sec (X1a,b,c, X3c, X6) the P′-R′ intervals are 0.21 to 0.25 sec; when the P,X intervals are 0.65 to 0.75 sec. the P′-R′ intervals are 0.28 to 0.32 sec (X3b); when the P,X and P′X intervals are 0.88 to 1.16 sec (X1h,i,j and X2d,e,f) the P′-R′ intervals are 0.31 to 0.38 sec. The slight difference in P′-R′ between X3b and X3c is crucial and determines whether or not a second reciprocal cycle occurs. Since all other conditions are similar between X3b and X3c this seems a critical test of the effect of the interval from the preceding atrial systole. Similarly, the difference in P′-R′ between X2d,e,f and X6 determines whether a second reciprocal cycle occurs, and the P′-R′ in turn seems to depend on the interval from the preceding atrial systole, since other conditions are similar. The interpretation is that P′-R′ is determined by the penetration of some part of the return path in the A-V node "near" the atria in terms of conduction time, or in the atria. This would explain the similar time relation of atrial systole to ventricular premature systole whether the return path is reached from above by a sinus impulse (X1a,b) or from below by a retrograde impulse (X1c).

Concealed Conduction: The influence of systoles not manifestly conducted on subsequent conduction time has been called "concealed conduction."[16] The effect of nonconducted atrial systoles just discussed is an example. In Table I there are a number of instances in which the previous nonconducted atrial systole determines subsequent events and whether or not reciprocal rhythm will occur (X1a,b, X2d,e,f, X3b,c). Ventricular premature systoles not conducted to the atria have the same effect as those that are conducted (X1b compared with X1c, X1e compared with X1f). These nonconducted ventricular systoles penetrate the A-V node, discharge it and determine the subsequent conduction time.

Relationship of V-A and P′-R′ Times: In previous studies of reciprocal rhythm[5,6] the time from the retrograde P wave to the next QRS produced by reciprocal rhythm (P′-R′) has been found to be inversely related to the V-A conduction time. This is to be expected when there is enough variation in the V-A conduction time and P′-R′ to test the relationship, and when the relationship is due to the fact that the return impulse has to cross a relatively refractory juncture, common to both the retrograde and return paths. This was observed in case 1 of this study. In cases 2 and 3 the data were inadequate to test the relationship. In case 4 the range of the V-A conduction time or P′-R′ for a given order of magnitude of V-A conduction time is too narrow to test the relationship. As regards the orders of magnitude of V-A conduction in case 4 there definitely is no relation to P′-R′. The latter is determined by other factors which have already been discussed.

PAROXYSMAL TACHYCARDIA

Reciprocal rhythm is a demonstrable circus rhythm, and herein lies a large part of its theoretic interest. In cases 1 and 3 single cycles of reciprocal rhythm occurred. In case 4 there were two cycles and in case 2 paroxysms of tachycardia. The simultaneously recorded esophageal and standard leads prove that this tachycardia is due to reciprocal cycles initiated by a ventricular premature systole (Fig. 5A). Without the simultaneous esophageal lead one might suppose that this is an ordinary atrial tachycardia, that preceding the complex which is called a ventricular premature systole there is a buried P wave ini-

tiating the tachycardia, and that the so-called ventricular premature systole is nothing more than aberrant A-V conduction from this first ectopic atrial systole. The simultaneous esophageal lead shows that there is no P wave preceding the ventricular premature systole.

Against the possible interpretation that the tachycardia illustrated in Figure 5 is from a repetitive nodal focus with aberration of the initial complex are: (1) the occurrence of three distinct types of ectopic QRS complexes initiating the paroxysms of tachycardia, (2) the occurrence of the ectopic QRS complexes during the tachycardia suggesting a parasystolic ventricular focus (Fig. 7), (3) the termination of each run of tachycardia with QRS complex, and (4) the occurrence of the tachycardia only after sufficiently long V-A conduction time or a sufficiently long interval from the ventricular premature systole to an immediately following P wave.

The interpretation of reciprocal rhythm and tachycardia initiated by a ventricular premature systole seems clear in Figure 5A where the retrograde P wave following the premature systole is definite. In Figure 5B where a sinus P follows the premature systole the same interpretation is possible if the bypass is below the atrium. If other conditions were constant, a constant interval from the premature systole to the next ventricular systole (X-R′) would be a test of the interpretation that the ventricular premature systole initiates the reciprocal rhythm and tachycardia. There was considerable variation in R,X and preceding P,P, however (Fig. 6), which may account for the variation of X-R′ from 0.60 to 0.71 sec for the nine episodes of tachycardia after the ectopic focus illustrated in Figures 5A and 5B. The time from the premature systole to the next QRS presumably produced by reciprocal rhythm for the three episodes of tachycardia after a second focus (Fig. 5C) was 0.58 to 0.59 sec.

Another possibility for Figure 5B which cannot be excluded with the available data is that the P after the ventricular premature systole is conducted to the ventricular systole following it and the paroxysm of tachycardia then follows by reciprocal rhythm. This is discussed in the following section, for an instance in case 4 where there is more evidence for such a mechanism.

It is not known how often tachycardia occurs as a result of reciprocal rhythm. The only other convincing report of a similar tachycardia initiated by a ventricular premature systole that the author could find is that of Bix.[2]

RECIPROCAL BEATS AFTER DELAYED A-V CONDUCTION

When the P of sinus origin in case 4 occurred 0.41 to 0.43 sec after R it was followed by the constellation of complexes illustrated after the third P of Figure 15. There were ten such sequences. One explanation is that the impulse of sinus origin is conducted, and reciprocal rhythm occurs as illustrated and explained in Figure 14. The similarity to the double reciprocal cycles after X3 in Figure 15 is apparent. P-R times were 0.32 to 0.36 sec, R-P′ 0.42 to 0.47 sec, and P′-R′ 0.21 to 0.22 sec. The similarity to the corresponding intervals of X1h, i, j (Table I), namely P′-R′, R′-P″, and P″-R″, is apparent. An alternate interpretation is that the nodal systole represented by the third R of Figure 15 was conducted retrograde, that it activated the bypass and produced the fourth R as a reciprocal beat, and that the sinus impulse (third P of Figure 15) was blocked because it arrived at the bypass soon after the activation of the latter (R-R′-P″-R″, Fig. 14).

Reciprocal Rhythm Following Conduction of Sinus Beat: The evidences in favor of the first interpretation, namely P-R-P′-R′ of Figure 14, are these:

(1) The P (third P of Fig. 15) showed no evidence of fusion in any of the 10 sequences under discussion.

(2) The minimum effective R,P interval for the sequence (third R to third P of Fig. 15) was 0.41 sec, just greater than the R,P interval, 0.38 to 0.40 sec, associated with concealed conduction into the A-V node from the sinus impulse. The evidence for the latter was the occasional occurrence of retrograde conduction from A-V nodal systoles that followed R,P intervals of 0.38 to 0.40 sec (Fig. 13). In one consecutive period of study there were 6 A-V nodal systoles which initiated retrograde conduction to the atria, and these followed R,P intervals of 0.38 to 0.40 sec (Fig. 13). Seven A-V nodal

systoles followed R,P intervals of 0.38 sec to 0.40 sec without initiating retrograde conduction. Fifty A-V nodal systoles followed R,P intervals of 0.16 to 0.37 sec and did not initiate retrograde conduction. The interpretation is that the sinus impulse sometimes penetrated into but did not discharge the A-V node immediately before recovery of the node and in some way affected the fast pathway so that it responded to the next A-V nodal systole with retrograde conduction to the atria. Concealed conduction occurs immediately before recovery of the A-V node, and Langendorf[16] predicted that the effect on subsequent conduction might be enhancement as well as depression of conduction.

(3) The P-R-P′-R′ sequence followed X1 three times and X2 once. In X1h,i,j the interval for reciprocal rhythm from X1 to A-V node to bypass and back to ventricle (X1-R′), was 0.84 to 0.89 sec. If the R following X1 in the three sequences under discussion were due to reciprocal rhythm a similar X1 to R interval should be expected. Instead it was slightly less, 0.80 to 0.81 sec. The differences are slight and the numbers of instances small, but the suggestion is that the sinus impulse reached the bypass a few hundredths of a second before the impulse from X1. Once the activation occurred by way of the sinus impulse the remainder of the cycle was the same (compare R-P′-R′ of Fig. 15 with R″-P″-R″). Similarly, one P-R-P′-R′ sequence after X2 was associated with an X2 to R interval of 0.89 sec compared with 0.90 to 0.94 sec for X2-R′ of X2d,e,f.

Other electrocardiograms which may be interpreted as reciprocal rhythm initiated by A-V conduction ("reversed reciprocal rhythm") are those described by Wolferth and McMillan,[33] Bix,[2] Katz and Pick,[13b] and Soloff and Zatuchni.[32] The phenomenon has been produced experimentally by Moe and his associates.[24] The rapidity of V-A conduction in two of these[13,33] has been considered an objection to the interpretation,[32,33] but it has been demonstrated that V-A conduction may be rapid.[15] In fact, if the concept of multiple pathways is valid one should expect to find instances under special conditions in which A-V conduction occurs along a slow pathway and returns to the atrium by way of a fast pathway.

Reciprocal Rhythm Following Retrograde Conduction and Activation of Bypass: It is necessary to consider the alternate explanation (R-R′-P″-R″ of Fig. 14) because it has been demonstrated that reciprocal rhythm may occur without evidence of retrograde conduction.[5,8,17,18,26] The explanation is that the bypass may be below the atrium, in the A-V node or bundle of His. The alternate explanation (R-R′-P″-R″, Fig. 14) cannot be disproved. P-R-P′-R′ is preferred in case 4 for the reasons given. So far as the hypothesis of multiple pathways and reciprocal rhythm are concerned there is little difference between the mechanisms P-R-P′-R′ and R-R′-P″-R″. In both the slow pathway is occupied by retrograde conduction at a time when the fast path is refractory. Whether the fast pathway is then activated by the original retrograde impulse or by the incidentally occurring sinus impulse depends on which reaches the bypass first. Once the fast pathway is activated the remainder of the reciprocal rhythm is the same. Both mechanisms may occur at different times in the same patient. The author believes that this is so in case 4. Possibly it is true also in case 2.

Summary and Conclusions

The mechanisms determining reciprocal rhythm initiated by ventricular premature systoles are analyzed on the basis of considerable data obtained in four cases by means of simultaneous esophageal and standard electrocardiographic leads. These are (1) delayed retrograde (V-A) conduction permitting recovery of a common path to respond to a returning impulse, (2) multiple pathways with different conduction times and refractory periods, (3) long preceding cardiac cycles, (4) early prematurity of the ventricular systoles, (5) delayed V-A conduction after a number of ventricular premature systoles in succession, and (6) the effect of timing in relation to previous atrial and ventricular systoles, including the mechanism of concealed conduction.

In one case there were two reciprocal cycles, and in another case there were repeated cycles producing paroxysmal tachycardia.

The concept of multiple pathways as a mechanism in reciprocal rhythm is developed in

detail on the basis of unusually many and varied events in one of the cases.

In one of the cases there was also reciprocal rhythm following A-V conduction.

Acknowledgments

The author thanks Drs. Harold H. Bix, Milton Landowne, and Richard Langendorf for critical study of the original manuscript. A number of their suggestions were adopted in the final manuscript. They do not necessarily accept the author's views. He also thanks Mr. Glen Moran, Mr. Luigi Palumbo, and Mrs. Mabel Reeder for technical assistance; and Dr. A. D. Belton for the opportunity to study the patient in case 3.

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Seminar on Ballistocardiography*

The Three-Plane Ballistocardiogram in Heart Failure†

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THE SIMPLE ballistocardiographs used in the pioneer era, 1937–50, recorded only head-foot movement. Because the shin or a footboard was the point of impact, these devices were sensitive to the forces generated in or transmitted to the caudal part of the body. In subjects beyond the age of 50, they often showed deep K waves at the end of systole and very large respiratory variations in IJ, the main systolic headward wave. With the onset of myocardial disease associated with hypertension, valvular, or coronary disease, there often was an increase in relative height of H, giving the "early M" pattern, or of L, the "late M" pattern. The correlation between these changes and such indices as dyspnea, gallop rhythm, or pulmonary hyperemia and edema was not clear-cut. Patients with coronary disease or hypertension, free of symptoms or signs of heart failure, sometimes showed abnormal head-foot ballistocardiograms. On the other hand, patients with severe congestive failure, barely able to be flat long enough for records to be inscribed, might show normal systolic patterns, with waves of large amplitude. In general, patients with high pulse pressures due to aortic reflux, A-V shunts, uremia, anemia, beriberi, or hyperthyroidism had large normal systolic waves even in heart failure, while those with small pulse pressures and small pulsations of hilar vessels had low amplitude "M" patterns.

With development from the naive recording systems of the pioneers toward the sophisticated device which records acceleration of a subject in almost aperiodic suspension, there has been a great change from this early situation. In the head-foot plane, respiratory variation in IJ waves is never marked, large H and L waves in disease have practically disappeared, and there is about as little difference in the ballistocardiogram in youth and age, or health and disease, as there would be in the brachial pulse curves. Even when one records head-foot motion with a sort of reversed Starr table where the shoulders are firmly held against a device for sensing head-foot displacement, the deep K becomes shallow, respiratory variation in IJ is small, and variation between old and young, between normals and those with healed infarction, is not striking. A patient whose IJ waves during expiration almost disappeared if he smoked on a Starr table usually shows very little change if he smokes while he is on one of the aperiodic suspensions.

* This issue contains Part VI of the Seminar on Ballistocardiography (edited by Sidney R. Arbeit, M.D.). A schedule of the articles already published, and of future articles in this seminar, may be found on pp. 101-102 of the January, 1959, issue (Vol. III, No. 1).

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Effect of Aging on Force at Shoulder and at Ischium

If one wedges a normal subject firmly between a shoulder yoke and a plate shaped like a bicycle saddle pressed against the ischial tuberosities, so that head-foot motion is recorded independently from these two points of compression of the trunk, the curves from men under 40 show only slightly lower K at shoulder than at ischium. However, with many men over 50, there is a strikingly deeper K, and much larger respiratory variation in IJ in the curves from ischium than in those simultaneously inscribed from the shoulder (Fig. 1). To get waves of comparable size, the sensitivity of the ischial pick-up must be two to four times that at the shoulder, because the forces from the lower part of the trunk or legs, which inscribed the familiar Starr pattern, are actually much weaker than, as well as different from, those inscribed from the shoulder. The aperiodic accelerometer curves from the whole body closely resemble the shoulder displacement seen in the curves of Figure 1.

The curves of shoulder displacement and of acceleration of the body in aperiodic suspension are apparently due mainly to forces arising in the aorta, with some force from the pulmonary artery. The Starr pattern, in older subjects, seems to be due chiefly to forces evoked by right ventricular ejection, for there is a large increase of IJ during inspiration, when pulmonic stroke volume increases up to 50 per cent. The shoulder or aperiodic accelerometer curves show very little increase in IJ during inspiration, but the fact that they show no inspiratory decrease, at a time when left ventricular stroke volume decreases slightly, shows that pulmonic arterial forces also contribute to these curves.

Methods of Recording Three-Plane Ballistocardiogram

In this presentation, we will deal only with Starr pattern of head-foot force, as obtained by light coils in a magnetic field at the level of the shins, and with lateral and dorsoventral force recorded from a platform under the thorax with side supports snug in each axilla. The platform is held by stiff springs, and motion is sensed by coils in magnetic fields.[1] These velocity curves are all integrated by condensers across the output, and the peaks and troughs in the head-foot plane closely correspond with those from the Starr table or in displacement curves of the shins as recorded photoelectrically.[2] Headward, backward, and rightward force is seen as upward deflection of the traces.

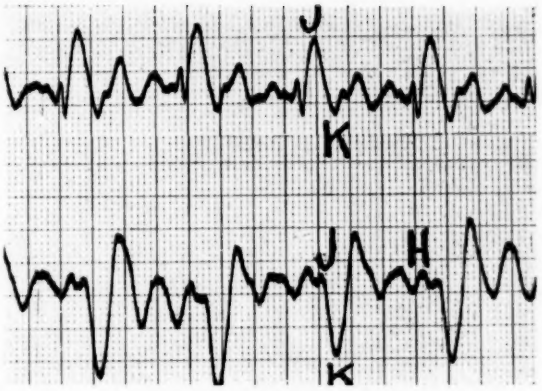


Fig. 1. Simultaneous head-foot ballistocardiograms from a 59-year-old man, wedged between a yoke on the shoulders and a seat plate on the ischial tuberosities. The upper curve is from the spring platform of the shoulder yoke, the lower curve from the ischial platform. Sensitivity of latter is twice that of shoulder. Taken in held expiration; during inspiration shoulder IJ increased 30 per cent, ischial IJ over 500 per cent.

Over the past six years, we have been convinced that, regardless of the naiveté of such apparatus, the head-foot trace gives more information of clinical value than shoulder or aperiodic accelerometer curves. It shows large variations with age and disease. Cigarette smoking, which has no effect on the pattern in normal young subjects, does produce striking changes in the head-foot pattern of more than half those whose other findings, including blood cholesterol levels, make coronary disease a certainty or strong probability.[3] Such changes are much less evident in shoulder or aperiodic accelerometer curves, or in curves of lateral and dorsoventral motion of the thorax. Lateral curves from older subjects may show respiratory variations in systolic force which are the reverse of those in the head-foot plane.[1,4] In a few kyphotic and emphysematous men, the dorsoventral curves resemble the usual head-foot pattern of HIJ waves, and show similar changes with respiration or smoking. While these head-foot curves are very different from those recorded with accelerometers on the aperiodic platform, the lateral curves are not very different from

those of lateral force obtained with accelerometers at the shoulder level, when lateral motion at the feet is restrained.

Terminology for Waves

In this presentation we do not use "M" as label for the pattern with large H or L waves, and will indicate wave forms, as in electrocardiography, by using lower case letters for small, upper case for relatively large, waves. Thus, the normal pattern is *hiJklmn*, the "early M" is *HiJ*, the "late M" is *JkL*. The pattern in free mitral insufficiency is *hijklMn* or *MN* (Fig. 2), while the classical pattern in coronary disease is *hijj'K*. In the latter a small ripple with three peaks replaces the normal *hiJ* complex. The peaks and troughs of the dorsoventral pattern usually coincide in time with those of the head-foot trace but deep frontward K waves are rarely seen. The H peak is normally equal to J in the lateral, and synchronous with headward H, but the lateral J is usually later and has a broader summit than in the other planes. Thus, lateral I may be at its lowest point when headward J is approaching its peak, and the lateral J may be at its plateau when footward K is inscribed. This asynchronism in waves in different planes, a commonplace in electrocardiography, has caused some difficulty to ballistocardiographers. Our experience indicates that there is no reason to expect peaks of mechanical force to coincide in three planes, any more than we would expect the electric forces to be synchronous in three planes. The forces which cause or contribute to the waves may differ in different planes.

The first waves headward, rightward or backward, following the Q wave of the electrocardiogram, are called H in all planes; those with headward, rightward or backward peaks 0.16 to 0.28 sec after Q are called J; and the headward force starting after the end of T is called L. So much for the technics and conventions in use at the laboratories at Kings County Hospital and at the Palo Alto Medical Clinic, from which our figures and information have been derived.

Heart Failure and Myocardial Failure

Heart failure, for our purposes, may be defined as the situation existing when one or both

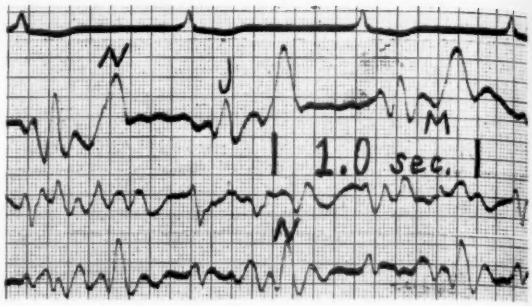


Fig. 2. Here and in subsequent traces, the ballistocardiograms are taken with head-foot at top, lateral in middle, dorsoventral at bottom. From a 40-year-old woman with atrial fibrillation and mitral insufficiency. The protodiastolic MN dominates, but unlike most cases is smallest in the lateral plane.

ventricles cannot maintain the stroke volume imposed by venous return without a sustained rise in end diastolic pressure. Heart failure, so defined, includes constrictive pericarditis and heart tamponade from pericardial effusion. Myocardial failure is the special instance in which diastolic pressure is high even in early diastole and the ventricular volume, as well as diastolic pressure, is above normal at the end of diastole. In pericardial embarrassment, diastolic pressure dips low in early diastole and the end diastolic ventricular volume is normal, reduced, or even increased in cases combined with myocardial fibrosis.

When myocardial failure is associated with high diastolic pressure in the artery supplied by either ventricle, or when stroke volume imposed by venous return is high, the failing ventricle must be doing more work per beat than normal. In such cases the ventricle is like a man who tires under a heavy burden or a steep climb, which he formerly handled without distress. In these situations, and even more when stroke volume and arterial pressure are normal or low, the myocardium has suffered a loss of efficiency or competence in its contractile function. In myocardial failure systole is prolonged in relation to total cycle length, and diastolic fiber length, myocardial heat production, and chemical turn-over rates are high in relation to the mechanical work performed. Clinical experience has shown that ventricular efficiency can be impaired by the salt-retaining adrenal steroids or even by high-salt diets, and it can be

improved by sodium depletion or by glucosides of digitalis, squill, or strophanthus.

Ballistocardiography can only reveal changes in the kinetic hydraulic forces. Since heart failure may or may not impair velocity of systolic ejection but does elevate atrial and venous pressure, it must inevitably cause an increase in force and velocity of protodiastolic flow from atria to ventricles. These inflow phases are usually shorter than normal in heart failure, and kymograms show ventricles which fill more rapidly than they empty. The force of atrial systole also may be increased, and hence the velocity of presystolic inflow may rise. Rapid inflow is not peculiar to myocardial failure—the same thing occurs when there is systolic reflux through an A-V valve or the semilunar valves, or when the ventricle is embarrassed by pericardial tamponade or constriction. Indeed, rapid inflow occurs in normal subjects when exercise, excitement, nicotine, or fever increases venous return, so that the phenomena of heart failure are exaggerations of those seen, in less marked form, under heavy physiologic loads in normal hearts.

Interrelations of Angina and Heart Failure

Clinicians have long been aware that angina usually decreased or disappeared when heart failure set in, and that most patients examined during anginal seizures had no evidence of myocardial failure—no gallop sounds, no fading of first sounds, no evidence of moisture in the pulmonary alveoli. Yet occasionally gallop rhythm or pulsus alternans is noted during anginal seizures, disappearing with relief from nitroglycerin. One of the most important evidences of the sensitivity of the ballistocardiographic method is that almost every bout of angina, occurring during recording of head-foot traces by Starr's method, is accompanied by very striking changes in pattern.[5] In many cases, as discussed elsewhere in this Seminar, the change involves only the IJK complex and can be interpreted as evidence of altered ejection. But in nearly all severe or prolonged bouts of angina, the entire pattern is disturbed, and there are large protodiastolic, presystolic or large early H waves. These can only be interpreted as evidence for myocardial failure, with a rise in pulmonic venous pressure, with rapid, brief inflow causing the transient increase in size of the protodiastolic and presystolic ballistic waves during the anginal attack (Fig. 3).

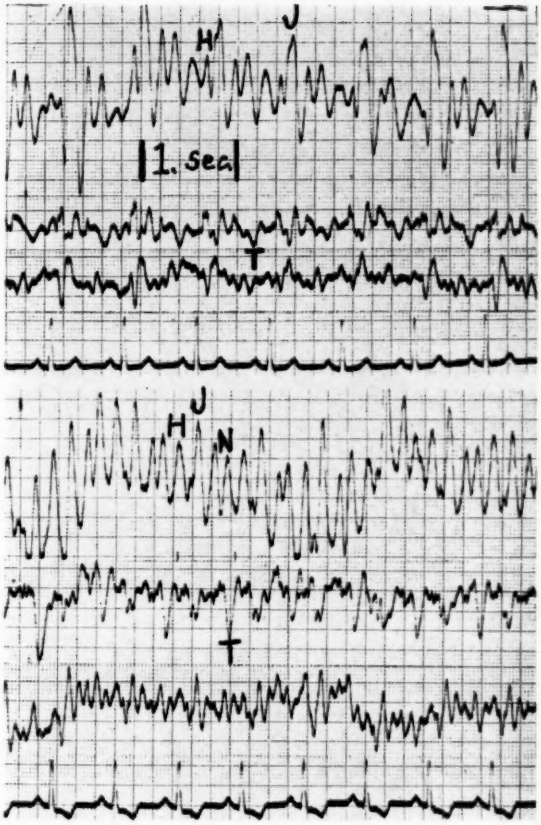


Fig. 3. Angina pectoris. During the attack of angina (lower set of traces) the large headward H and a diastolic leftward thrust synchronous with P are striking features. Between attacks (upper set of traces), J is notched during expiration, the trace is normal in other respects. The headward H during attack begins before Q. Before the attack the small diastolic leftward thrust (T) precedes P, and H follows Q. Thus a great increase in late protodiastolic force and in presystolic force is evident during the attack.

The phenomena seen in chronic heart failure also appear as transient effects of cigarette smoking in some patients known to have recovered from clinical episodes of coronary disease, and in young people who show very fast rates and large systolic forces on smoking. The former usually show striking changes in systolic waves during the expiratory phase after smoking (Fig. 4), while the young normals, sensitive to tobacco, do not. The large diastolic waves in the latter group probably are due to high rates of

blood flow, not to myocardial damage due to coronary vasoconstriction (Fig. 5).

In this report, we shall deal with prolonged and painless heart failure, but it is necessary to emphasize that ballistocardiography has revealed much greater myocardial impairment during anginal seizures than had been suspected from clinical observation. Also, it must not be forgotten that a few puffs on a cigarette by a patient with coronary disease may cause changes in the ballistocardiogram even when no pain or electrocardiographic changes occur. These effects of the cigarette may include protodiastolic waves similar to those occurring in myocardial failure.

The Changes in Pattern Seen in Heart Failure

Changes in IJ Wave: The only change in the systolic IJ wave which can with confidence be ascribed to myocardial failure is alternation, first recorded by Starr[6] in his Figure 1, second row. This has the same significance as pulsus alternans, and like it may be especially marked in the first few cycles after an ectopic beat, as in Starr's patient. When no alternation can be demonstrated in carotid pulse curves, the alternation in ballistocardiographic IJ must be ascribed to right ventricular failure with alternation in pulmonary arterial flow and pulse pressure. Other changes in IJ, notching of J, decrease in amplitude, may occur during heart failure and also with many other conditions such as bundle branch block and hypertension causing differences in ejection velocity, or shunts causing differences in volume flow of the two ventricles. However, notching of J or low amplitude IJ which is corrected with digitalization or sodium depletion can be ascribed to myocardial failure. This evaluation can only be made from serial traces by one familiar with the clinical features and treatment.

Changes in Atrial (Presystolic) Waves: In sinus rhythm, the effect of atrial forces can be established only in cases of complete heart block. As reported by us previously[7] (Figs. 10 and 13 in that publication), the head-foot waves due to atrial systole may be large, but in most cases the lateral waves are the largest. The situation shown in Figure 6 is noteworthy because the

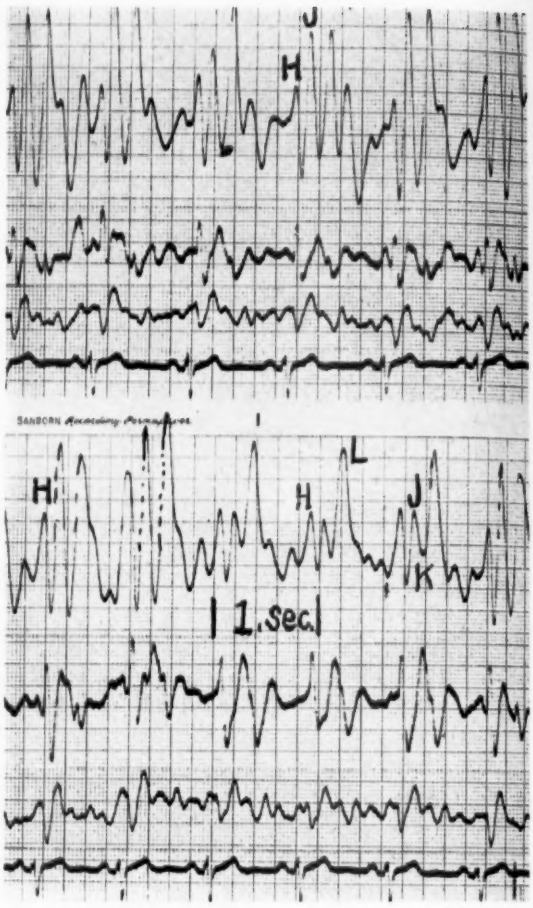


Fig. 4. Effect of smoking in angina. The upper curves show the control, lower the effect of smoking, in a man, 42 years of age with angina. The first two beats, in inspiration, show increase in H waves, but the third, fourth, and fifth beats, during expiration, show great decrease in J and K after five puffs on a cigarette. The large L wave persists even though the systolic forces in expiration are markedly diminished. The lateral and front-back forces are increased by smoking, but otherwise unaltered.

atrial waves, small in two planes, are very large in the lateral trace, while a protodiastolic gallop, causing relatively small lateral force, produces large waves headward and backward. Thus rapid passive early diastolic filling and filling due to atrial systole may have quite different vectors of force. Atrial systole is followed by two headward, rightward, and backward peaks, about 0.1 and 0.25 sec after P, and the second wave is usually much larger. When P-R intervals are less than 0.18 second in sinus rhythm, such waves may coincide with the H wave of ventricular systole. These

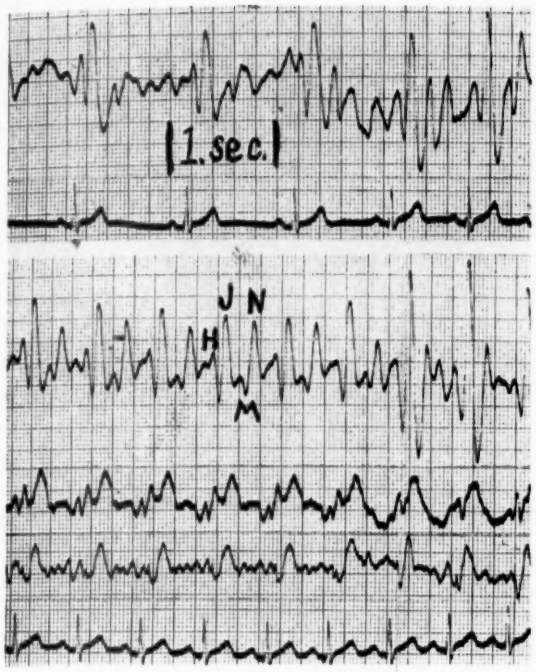


Fig. 5. Effect of smoking on an obese woman, 26 years old; no cardiac disorder. The control head-foot trace and lead II above. Below, the effect of five puffs on a cigarette; first five cycles in gentle expiration, last two cycles in inspiration. Marked acceleration of rate and increased systolic force during inspiration, as well as a large MN wave and shortened K, are produced by smoking. These effects may all be due to pressor, accelerator, and venopressor actions of nicotine.

forces are increased in heart failure and angina, and probably are the cause of most large H waves which are so often seen in these conditions. However, large H waves also occur in some cases of atrial fibrillation, becoming larger during exercise and smaller after effective therapy. Therefore, purely ventricular forces, probably associated with motion of an abnormally large ventricular blood volume in isometric contraction, also play a part in causing large H waves and the "early M" pattern.

In some cases with severe failure or long P-R intervals, there may be a presystolic atrial wave which returns toward the base-line before Q, and H following Q may also be large. Only when a large H has its upstroke start before Q can it be ascribed to atrial activity and regarded as equivalent to presystolic gallop, but any H which is equal to or larger than headward J is abnormal and evidence of myocardial embarrassment in cases without valvular disease.

Mitral and tricuspid stenosis, with no evidence of myocardial failure, may cause large presystolic *a* waves when P-R is prolonged, or large H waves at normal P-R intervals. The large early headward forces are not specific evidence of failure, but only of very high velocity of flow through the A-V orifice. This may be due to a rapid flow and normal orifice, with a brief but

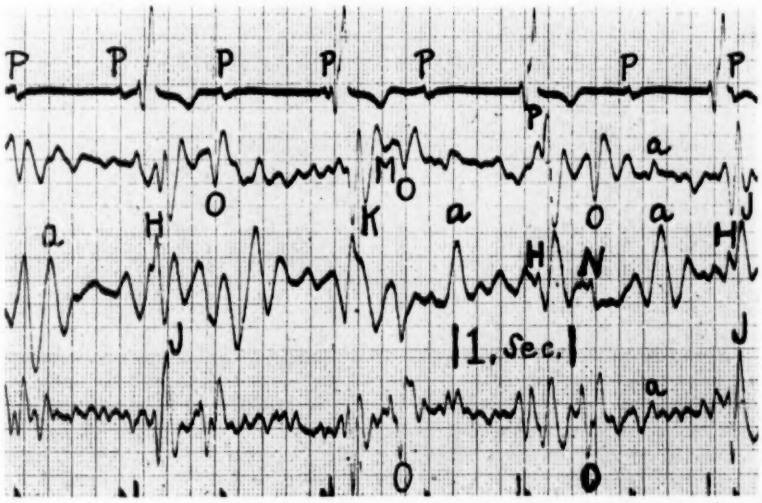


Fig. 6. Complete heart block. Only in the last beat can the ventricular hIJ pattern be seen free of atrial waves, and only the preceding atrial beat shows the pure atrial forces, with no interference from ventricular systolic or protodiastolic waves. Atrial forces are small except in the lateral plane, where the huge *a* waves reach a peak more than 0.25 sec after onset of P. In the first three ventricular beats the lateral h or J is almost lost in the atrial wave. There is a gallop wave, NO, which is small in the lateral plane and most striking in the dorsoventral trace.

rapid jet when pressure is elevated, or to a narrow orifice with sustained high velocity jet. The force varies here, as elsewhere, directly with the mass of blood but with the square of velocity. Only when stenosis of an A-V valve has been excluded can large H waves be accepted as signs of myocardial failure. In a number of cases of angina with bad prognoses, this was the chief anomaly in the ballistocardiogram taken at rest.

Abnormal K and L Waves: A fairly common finding in heart failure and in mitral stenosis is a tall headward L wave. When the latter is preceded by a very deep K, some of the L may be due to "bounce" or body resonance. This explanation does not fit the situation seen in Figure 4, where K is very short and L tall during expiratory phase of normal breathing. Occasionally, short K waves are the only abnormality in a patient with heart disease. If they approach normal on recovery, as in Figure 7, it must be conceded that late in systole or during isometric phase of protodiastole forces are developed which oppose the normal K or augment L, or both. This could be due to high end systolic ventricular volume and rapid rise of A-V septum, when the systolic contraction of papillary muscles dies out. This seems unlikely since the usual plane of the A-V septum is not horizontal but almost vertical. Large lateral waves usually are not seen with large headward L waves as would be expected if the force arose at the A-V orifice. One therefore can only point out that large headward L waves are often noted in heart failure (and in A-V valvular stenosis), and that short footward K waves are also seen in heart disease. Both tend to revert to normal with effective treatment. The cause for these changes remains obscure.

Large LM or MN (Protodiastolic) Waves: The only really dependable evidence of heart failure in the ballistocardiogram is augmented protodiastolic force later than the L wave. When these protodiastolic waves are equal to or larger than the IJ waves, in one or more planes, the significance is exactly the same as when protodiastolic gallop is heard or recorded, or when kymography or apex tracings show the ventricle refilling more rapidly in early diastole than it empties in systole. The largest wave usually is LM or MN; rarely, as in Figure 6, is it as late as O. This phenomenon, regularly seen in constrictive pericarditis, subendocardial fibrosis, or marked mitral systolic reflux, occurs in atrial fibrillation, when presystolic gallop phenomena cannot be present. Its absence in well-compensated atrial fibrillation is always a cheerful prognostic finding; its absence in a

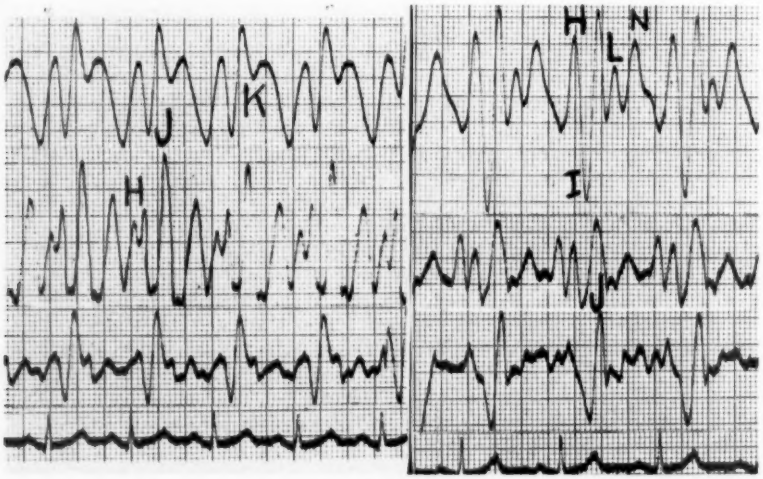


Fig. 7. Effect of improved clinical state, from a man with indigestion, five years after three severe bouts of anginal pain. The first set of tracings taken when rate was 96, blood pressure 150/100; the second seven months later, rate 70, blood pressure 120/80; weight down from 195 to 165 pounds. Headward H begins before Q, lateral H is reduplicated. I and K footward are much deeper as circulatory state improves; headward and backward IJ are larger and occur later, but lateral IJ is smaller. Notch in lateral K corresponds with headward L wave. Change in IJ vector may be due to lower diaphragm after weight loss.

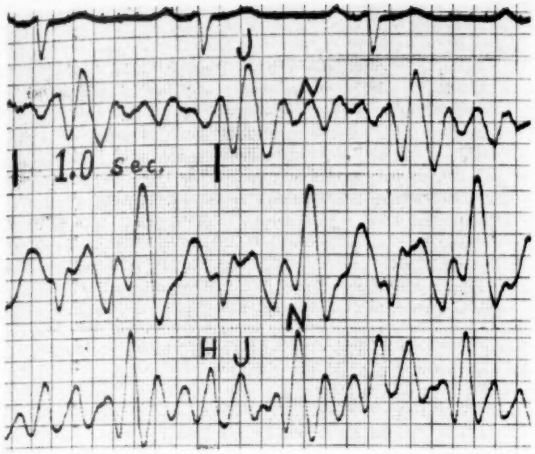


Fig. 8. Constrictive pericarditis, from a 67-year-old man with constrictive pericarditis, later relieved by operation. The head-foot trace is remarkably normal for this age, but the lateral and dorsoventral planes show very large protodiastolic waves.

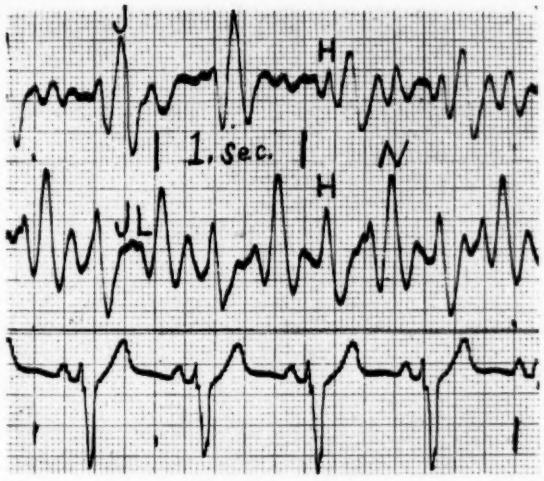


Fig. 9. Myocardial infarction and bundle branch block, from a 58-year-old man, with minimal heart failure in the presence of postinfarction bundle branch block and aneurysm of left lateral wall. The head-foot trace is normal, the lateral shows notched J, tall H and a large protodiastolic wave.

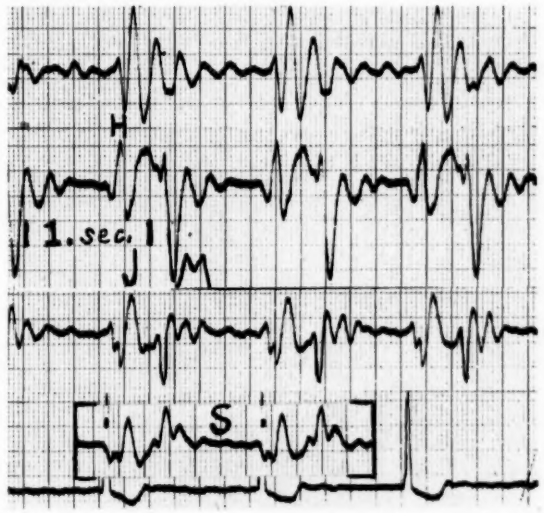


Fig. 10. Mitral insufficiency, from a woman, 27 years old, with well-compensated mitral insufficiency. The head-foot trace is normal as recorded from the shins, but the insert in the electrocardiographic strip shows two cycles from the head-foot curve recorded from the shoulder. Here the protodiastolic headward thrust is taller than J and coincides with the leftward and frontward M in the other planes. The "mitral" notch on HI shows here, but not at shins.

fibrillator having signs or symptoms of pulmonary engorgement raises a strong suspicion that pure mitral stenosis is present, for this lesion is incompatible with rapid protodiastolic inflow and deep M or tall N waves.

In the presence of marked tricuspid insufficiency, protodiastolic gallop or large M and N waves may be found even with a very tight mitral stenosis. It is only when these valvular or pericardial causes are excluded that protodiastolic gallop or large M to O waves can be taken as evidence of myocardial failure, overt or latent. This is seen in aortic valve disease and in hypertension with myocardial failure, as well as in myocarditis, beriberi heart disease, and other causes of myocardial overloading and failure. The most frequent cause is myocardial infarction, especially in private patients. In the city hospital population nutritional heart disease, uremia with anemia and hypertension, and hyperthyroidism with atrial fibrillation are relatively frequent, but hypertension and coronary disease, often with no history of chest pain, remain the most common causes of protodiastolic gallop phenomena.

As was noted by the Hopkins groups,[8] in pericarditis with constriction the protodiastolic waves of large amplitude are usually best seen in the lateral trace. The head-foot trace often is normal in cases of heart failure, mitral insufficiency, ventricular aneurysm, and constrictive pericarditis when huge protodiastolic waves are present in other planes (Figs. 8, 9, and 10). Only occasionally is a protodiastolic wave recorded in the shoulder head-foot trace, or in that from the aperiodic accelerometer, when the shin or Starr table trace is normal (Fig. 10).

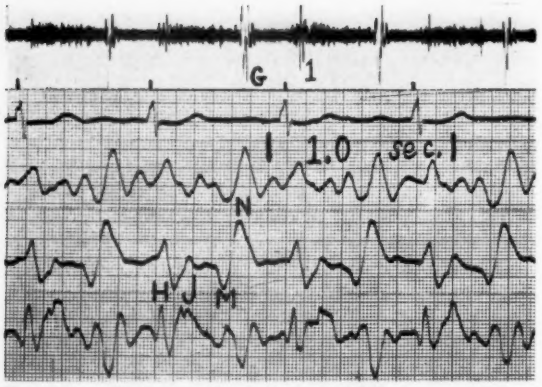


Fig. 11. Gallop with increased MN wave, from a woman, aged 43, with mitral insufficiency and atrial fibrillation treated with I^{131}. J is small and bizarre. Large protodiastolic force in all planes. This force acts ventrally, while acting headward and rightward, in this patient with a giant left atrium. The apical heart sounds, from a record taken the same day, and with R waves of the electrocardiogram marked with black dots, is inserted above to show the loud gallop sound, G. The first sound is followed by a murmur; the second sound is not recorded at the apex.

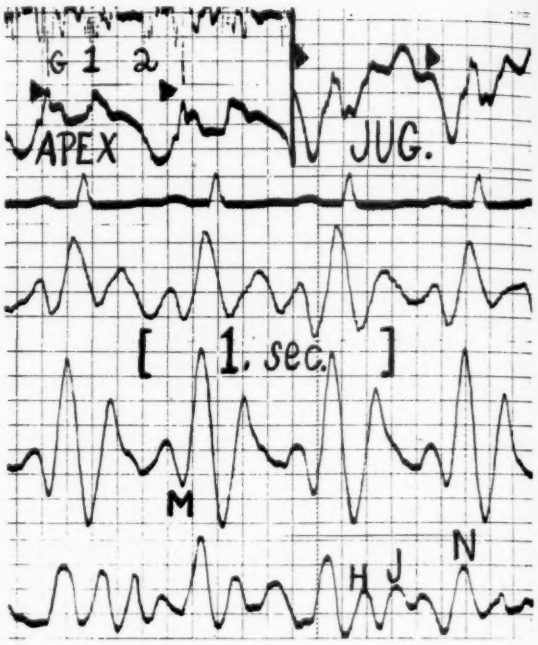


Fig. 12. Summation gallop with large MN waves, from a woman with hypertension and constrictive pericarditis. The apex beat and heart sounds (left upper) and jugular pulse (right upper) were recorded with electrocardiogram and position of P waves marked by black triangles before inserting above electrocardiogram recorded with the ballistocardiogram. Huge MN waves begin 0.16 sec after second sound; the gallop sound begins at 0.12 sec and is maximal at 0.16 sec, when the apical thrust in diastole is reflected and protodiastolic dip in jugular pulse is sharply reversed. The H and J waves are fused, except in front-back plane.

Even more unusual is a normal lateral trace when large protodiastolic waves are present in another plane. However, the fact that this does occur (Figs. 2 and 6) is further proof that the force axes of the heart, like the electrical axes, may shift over such a wide angle that records of either electrical or kinetic force in a single plane are inadequate. Significant forces may be present in one plane in one subject, in another plane in others, and in all three in a few (Figs. 11, 12, and 13).

Superimposed Atrial and Protodiastolic Waves: As is apparent in Figure 12, the protodiastolic force, when diastole is brief, may not be maximal until after atrial systole has begun, thus causing the ballistocardiographic equivalent of the "summation gallop" of the phonocardiogram. In Figure 13, although P-R is prolonged to 0.20 sec, the presystolic wave is distinct and presystolic only in one plane; in another its peak occurs after Q, while in the frontal plane, a large footward force, certainly of atrial origin, begins at O and H is maximal 0.13 second later.

Identification of Late Systolic and Protodiastolic Waves in Tachycardia: At rates over 120/min it becomes difficult to identify late systolic from protodiastolic waves, especially in the head-foot plane. Thus, in Figure 14, the K wave is maximal after onset of atrial systole, and headward L could pass for a large presystolic wave. This is the record of a vigorous man of 67, who had had asthma, emotional tachycardia and hypertension since his late twenties. The record indicates a large systolic force at a pulse rate of 118/min, certainly a high minute flow. The large dorsoventral and lateral IJ waves are characteristic of emphysematous men with tortuous aortas. The peak of J is 0.08 sec earlier backward than headward, 0.06 earlier than rightward. Death from cerebral arterial thrombosis, five months later, made it possible to confirm the absence of coronary disease or any cardiac abnormality except moderate thickening of both ventricles. The late J and K peaks, in this hypertensive man with tachycardia (Q-K = 0.43 sec), contrast strikingly with the early J and K in bradycardia with low diastolic pressures, in Figure 6 (Q-K = 0.30 sec), although the Q-H interval is the same, 0.15 sec, in both.

Without the dorsoventral trace it would be difficult to prove that the head-foot trace in Figure 14 did not consist of a deep LM, a large presystolic wave, and a small J wave, or small fused HJ. Thus a normal ballistocardiogram would be misdiagnosed as an extremely abnormal one, an error avoided in this patient by study of the dorsoventral pattern.

In Figure 15, a similar difficulty presents itself. This 64-year-old hyperthyroid man, with bouts of paroxysmal fibrillation, has a huge series of headward waves like those in Figure 14, except that J in Figure 14 is rarely equaled

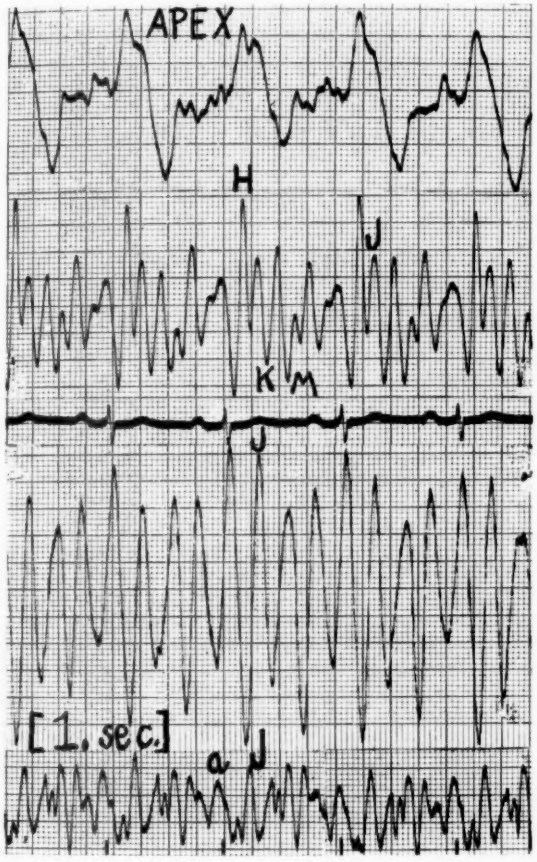


Fig. 13. Superimposed large atrial and early systolic waves, from a man with healed infarction, who successfully underwent abdominal aortic grafting. The upper apex curve is fitted to electrocardiogram taken with ballistocardiogram; it shows the sustained apical thrust of a ventricular aneurysm. A GH complex dominates head-foot trace; a huge HI, beginning before Q, is the main feature in lateral, while front-back shows distinct atrial *a* in presystole, small H after Q, normal J. The LMN protodiastolic wave is evident, but asynchronous, in all planes.

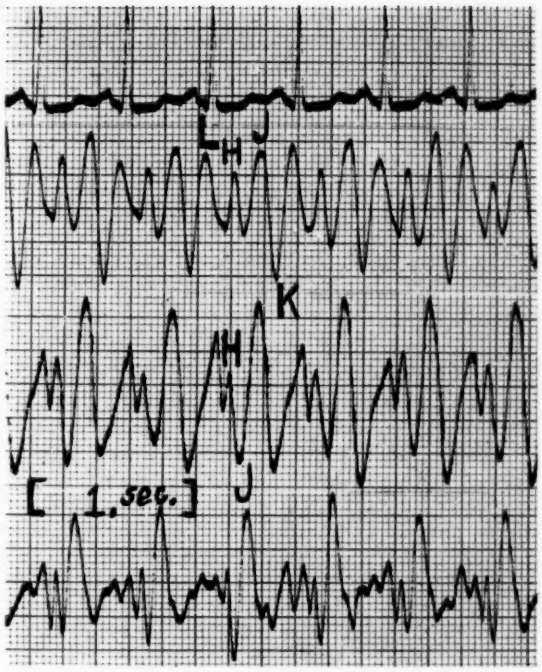


Fig. 14. Identification of ballistic waves in tachycardia. From a 67-year-old man with emotional tachycardia and emphysema. Discussion in text.

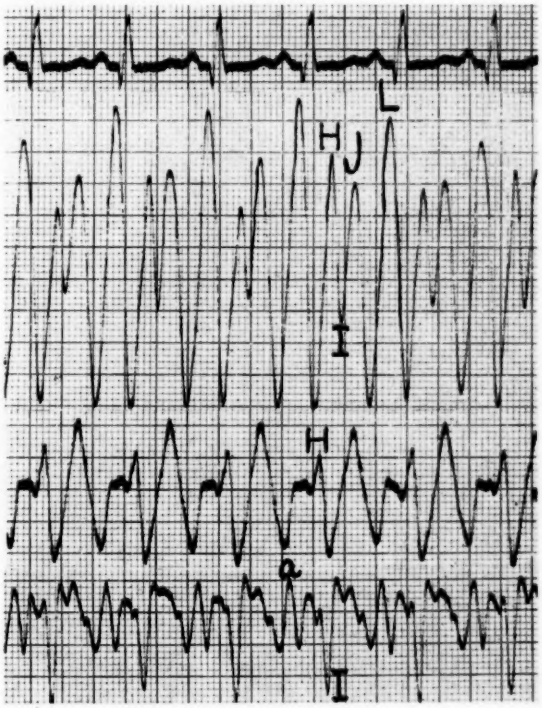


Fig. 15. Identification of ballistic waves in tachycardia. From a male, aged 64, with hyperthyroidism. Discussion in text.

by L, never equaled by H. In Figure 15, J never approaches L, is often exceeded by H. Here there is a large atrial wave in the dorsoventral plane and it seems safe to conclude that, in spite of the large stroke volume, myocardial failure is present as the cause of increased forces early and late in diastole.

Effect of Exercise: One of the most helpful ways to clarify the significance of curves of suspicious but not diagnostic abnormality is to observe the effect of stress or of therapy. Thus, in the upper traces in Figure 16, it is obvious that there is alternation in headward J, but the small second and fourth J waves occur after short cycles (0.85, 0.80 sec), the large J after a longer cycle (0.89 sec). However, in the lower trace, after moderate exercise, the tall fused HJ waves occur after short cycles (0.77, 0.82 sec). After the longer cycles (0.86, 0.90 sec), J is even shorter than before, and smaller than H. Alternation here is not a consequence of varying cycle length in a fibrillating, digitalized cardiac, but seems to be a true pulsus alternans, aggravated by exercise. Since the peak of the tall waves is 0.10 sec after Q, it is obvious that it is H rather than J which is alternating. The wave marked with ? may actually represent J, since its peak, 0.25 sec after Q, occurs at the same time as the J peaks before exertion. In any event, the change after exercise in this patient, with little rise in pulse rate, leaves little doubt that myocardial failure is present.

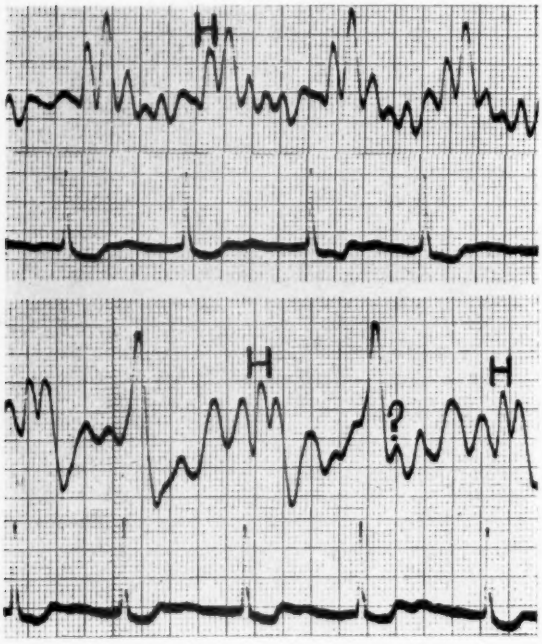
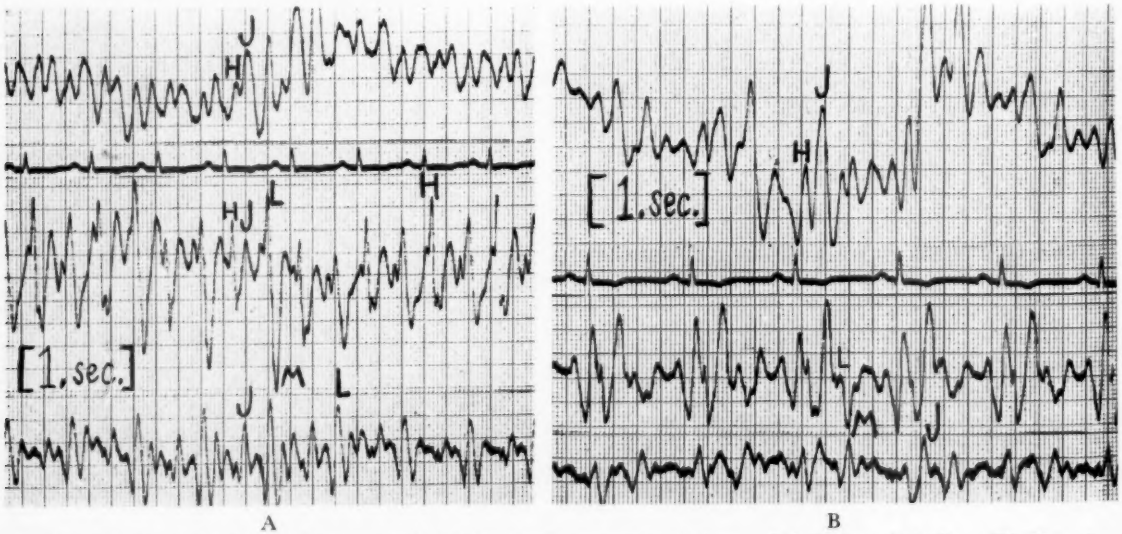


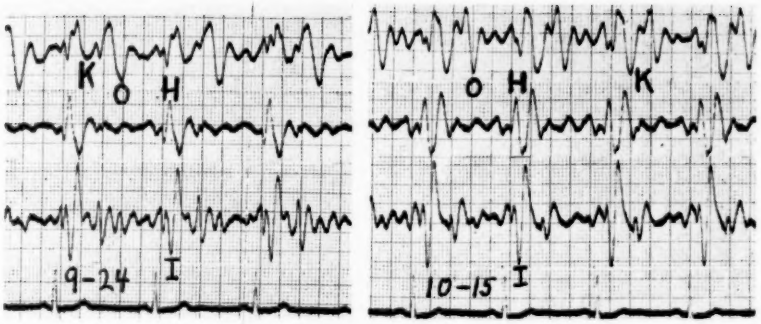
Fig. 16. Pulsus alternans (*upper*) accentuated by exercise (*lower tracing*). Discussion in text.

Effect of Digitalization: The increase in systolic force in cases of heart failure treated by intravenous injection of digitalis may be striking after some minutes (our Fig. 82;[7] de Soldati's Fig. 119[9]), and marked changes after digitalis by mouth have been reported by Starr (his Fig. 2.)[10] In three-plane tracings from our



A B

Fig. 17. Effect of digitalis. Postmyocardial infarction; congestive failure. (A) Before digitalis. (B) Ten days after digitalization. Discussion in text.



A B

Fig. 18. Effect of digitalis. Elderly patient with swollen ankles. (A) Before digitalis. (B) Two weeks after digitalis started. Discussion in text.

patients given digitalis (Fig. 9 in a previous publication[11]), it was found that disappearance or decrease in the protodiastolic waves was also a striking feature. This phenomenon is clearly shown in Figs. 17A and 17B, from a man who survived two bouts of myocardial infarction and later developed congestive failure. After 10 days on digitalis the rate fell from 100 min (Fig. 17A) to 70 (Fig. 17B), and there was striking improvement in breathing and decrease in fatigability. Huge diastolic waves in the lateral and front-back plane have almost disappeared, systolic waves markedly increased after digitalis in this ambulatory patient.

In Figures 18A and 18B another response to oral digitalis is apparent. This elderly woman had edema of legs when, as was her custom, she walked a great deal. There was no evidence of old coronary disease and little enlargement of the heart. Digitalis, in two weeks, led to increase in IJ, especially in lateral plane, reduced notching of headward J and greatly increased footward K. The area, but not the amplitude of head-foot MNOP, was reduced, but backward MN became more evident. This was one of the exceptional cases where protodiastolic force was not seen in the lateral plane, though it was equal to the systolic force headward. The large frontward IJ probably was related to kyphosis and emphysema. Here again the value of digitalis was made clear by the ballistocardiogram, although there was no change in the relatively slow pulse. This established the presence of myocardial failure which was not indicated by any other objective finding.

As in electrocardiography, trivial deviations from the normal ballistocardiogram may be the only objective evidence of disease in patients with disorders which may prove to be rapidly fatal, and very marked abnormalities may be present as constant findings for years in patients who are active and free of all symptoms. The physical and laboratory findings can only be evaluated by their rate of change in serial observations, and by meticulous comparison of all data, including a detailed and dependable history. There is no excuse for anatomic diagnoses or prognoses based on a single set of tracings of the electrical or kinetic forces of the heart, even when described by an experienced man, if he has no other data concerning the patient.

The study of the changes in the three-plane ballistocardiogram following digitalis therapy in patients with disorders which may lead to congestive heart failure has proved of value. Because gallop sounds often are difficult to hear or record in kyphotic or emphysematous men, demonstration of large protodiastolic forces may be the only evidence of latent failure in elderly patients. When the trace becomes much more normal on digitalis or on salt depletion, the value of prophylactic management seems to be soundly established.

Summary and Conclusions

A three-plane ballistocardiograph, using a small platform on springs placed under the thorax to record lateral and front-back force and the shin pick-up for head-foot force, gives a maximal amount of clinical information in cases of valvular, pericardial, or myocardial dysfunction.

The most significant changes are increased force associated with rapid protodiastolic filling and with isometric contraction in early systole, as well as increased force in presystole when the atria contract, but not in atrial fibrillation. Changes in height or form of the systolic IJ wave occur, but are less dependable evidences of heart failure. Shortening of K or increase in L wave can be ascribed to heart failure only when the abnormality is seen to disappear with digitalis or sodium depletion.

Since mitral valve insufficiency or constrictive pericarditis produce the same changes in early diastolic filling as myocardial failure, only excluding these diseases or the correction by medical therapy proves that myocardial failure is the main cause of such abnormalities in the ballistocardiogram.

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Case Reports

Postoperative Aneurysm of the Ductus Arteriosus

With Fatal Rupture of a Mycotic Aneurysm of a Branch of the Pulmonary Artery*

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ANEURYSM of the ductus arteriosus is a very rare lesion, and the majority occur in the newborn as a complication of the changes which normally lead to the closure of the ductus.[1] In the adult it is so uncommon that the subject is barely mentioned by Gould.[2] Three cases in adults have been described by Graham[3] and Mackler and Graham,[4] and at least three others have been recorded, but in none was trauma, surgical or accidental, considered to be the cause. Recently, Holman *et al.*[5] reported a case in which an aneurysm of the ductus resulted from two attempts at closure of the ductus by ligation only. The aneurysm was complicated by bacterial endarteritis which was not successfully treated by antibiotics. When the aneurysm was divided, the silk sutures from a previous operation were found at the site of the vegetations. In a report by Bonham-Carter *et al.*[6] their case 7 was thought to show a postoperative aneurysm of the pulmonary artery, but in view of the present report the possibility that the aneurysm seen on x-ray in their case arose from the ductus arteriosus cannot be excluded. The present case is remarkable in that embolism of ligature material occurred to the lower lobe of the right lung, causing a mycotic aneurysm of a branch of the pulmonary artery. This aneurysm ruptured into a bronchus, and fatal hemorrhage ensued.

It has recently become recognized that the typical auscultatory findings of patency of the ductus may be greatly modified in the presence of pulmonary hypertension. A number of cases have been reported[7,8] in which the diastolic murmur was absent due to the relatively low diastolic pressure gradient between the aorta and pulmonary artery. Very occasionally even a systolic murmur is not heard and rarely both systolic and diastolic elements may be absent.[9] Where typical clinical findings are lacking the correct diagnosis may depend on the findings at cardiac catheterization, but this method may fail if the aortic-pulmonary flow is small or reversed.[10]

Some observers have expressed doubt as to the advisability of closing the ductus in older patients who have marked pulmonary hypertension, and presumably pulmonary arteriosclerosis, particularly if the flow through the ductus is the reverse of normal.[7,8,10,11] The magnitude of the pulmonary arterial changes and the degree of hypertrophy of both ventricles in this case make it unlikely that any long-term benefit could

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have been achieved even if the surgical complications had not occurred.

Case History

M. S., a 34-year-old white woman, was first seen in May, 1952. Congenital heart disease had been diagnosed at the age of eight years, but she denied having had any symptoms until the age of 29 years when hoarseness appeared. Laryngeal examination at that time revealed left recurrent laryngeal paralysis which was attributed to her cardiac lesion. About the same time she began to have dyspnea on effort and shortly after developed atrial fibrillation and heart failure, for which she was treated in Winnipeg by Dr. F. A. L. Mathewson, with bed rest, sodium restriction, and digitalis. She improved greatly but still had dyspnea and palpitation on effort. Early in 1951, she had another attack of failure quickly relieved by diuretics.

When examined on May 30, 1952, her blood pressure was approximately 150/88 and she was fibrillating with a ventricular rate of 75 per minute. The heart was grossly enlarged to the left and there was a blowing grade III diastolic murmur along the left sternal border, propagated nearly to the apex. No systolic or other murmurs were heard. There were no signs of cardiac failure, and no cyanosis or clubbing was evident.

Fluoroscopy of the chest showed a very large heart with the left ventricle nearly touching the axilla and a greatly enlarged pulsatile pulmonary artery and dilated pulmonary artery branches with only slight hilar pulsation. Electrocardiogram revealed borderline right axis deviation, atrial fibrillation and digitalis effect, but no definite evidence of either right or left ventricular hypertrophy.

X-ray of the heart on July 21, 1952 (Fig. 1A), showed gross enlargement of both ventricles and of the pulmonary artery, the branches of which were also much dilated. A clinical diagnosis of congenital heart disease, probably an arteriovenous shunt, pulmonary valvular insufficiency and atrial fibrillation was made.

Catheterization Findings: Because of the possibility that she might have a patent ductus and that interruption of the ductus could be accomplished, cardiac catheterization was done on July 22, 1952. Difficulty was experienced in entering the superior vena cava because of kinking of the innominate vein and consequently the tip of the catheter was thereafter more difficult to control. The pulmonary artery was reached on several occasions but the catheter was repeatedly flipped back into the ventricle before pressure curves or specimens could be obtained. It was, however, observed on the oscilloscope screen that the systolic pressures in the pulmonary artery and right ventricle were approximately the same. The pressure reading in the right ventricle was 116/8 mm and in the right auricle 15/8 mm Hg. The oxygen saturations (in vol. %) were as follows: superior vena cava 14.8, right auricle 14.9, right ventricle 14.3; the oxygen capacity was 20.4 vol. %.

On the basis of the above data, it was believed that atrial and ventricular defects had been ruled out and that there probably was a very large ductus arteriosus. The absence of typical murmurs was explained on the basis of a high pressure in the pulmonary circuit nearly equaling that of the systemic circuit.

Operative Findings: At operation on September 24, 1952, the pulmonary artery was very large and under very high tension. No thrill was felt. A very short ductus, nearly an inch in diameter, was found and dissected out with great difficulty. It was considered too difficult and dangerous to divide the ductus, so each end was tied tightly with umbilical tape and two silk sutures were placed between. The lumen of the ductus then seemed to be completely occluded.

A sample of blood taken from the pulmonary artery before ligation showed an oxygen content of 19.4 vol. %, and after tying 16.5; the oxygen capacity at this time was 22.7 vol. %. A biopsy of lung tissue revealed marked proliferative endarteritis.

Postoperative Course: The immediate postoperative course was quite satisfactory, and she remarked the next day that palpitation had disappeared. However, she continued to fibrillate and no attempt was made to restore normal rhythm. Her exercise tolerance was not improved. X-rays of the heart on November 8, 1952, showed no change from the previous films. She was not seen then until April 21, 1953, when on routine fluoroscopy a large pulsating bulge was seen in the left upper heart shadow (Fig. 1B, C). The heart size and the appearance of the lung fields were unchanged from the preoperative film. In lateral and oblique films it was difficult to delineate the various structures but the aneurysm did not seem to be a part of either the aorta or pulmonary artery. It was therefore concluded that aneurysmal dilatation of the ductus had resulted from the operation, probably because the high tension had so injured the vascular wall at the site of ligature that recanalization had taken place. Operation was considered but rejected because of the technical difficulties of mobilizing the aneurysm and the fact that such extensive vascular sclerosis was evident in the lung biopsy sections.

Her clinical status and physical examination were not altered until about the middle of May, 1953, when she developed chills, fever, cough with scanty sputum, and rales at the left base. A diagnosis of pneumonia was made and she improved on treatment with penicillin. A week later her fever and cough recurred and she was admitted to the hospital on May 28, 1953. X-ray on May 29, 1953 (Fig. 1D) showed a mottled density, thought to be pneumonic, in the right lower lung. The heart, great vessels, and the aneurysm were unchanged in appearance. Examination showed the same loud diastolic murmur along the left sternal border, rales at both lung bases, atrial fibrillation with a rate of 90, and a blood pressure of 110/70. Her liver edge was felt 3 fingerbreadths below the costal margin but there was no pitting edema. A diagnosis of bronchopneumonia and cardiac failure was made. With penicillin and diuretics she made a gradual improvement and was discharged,

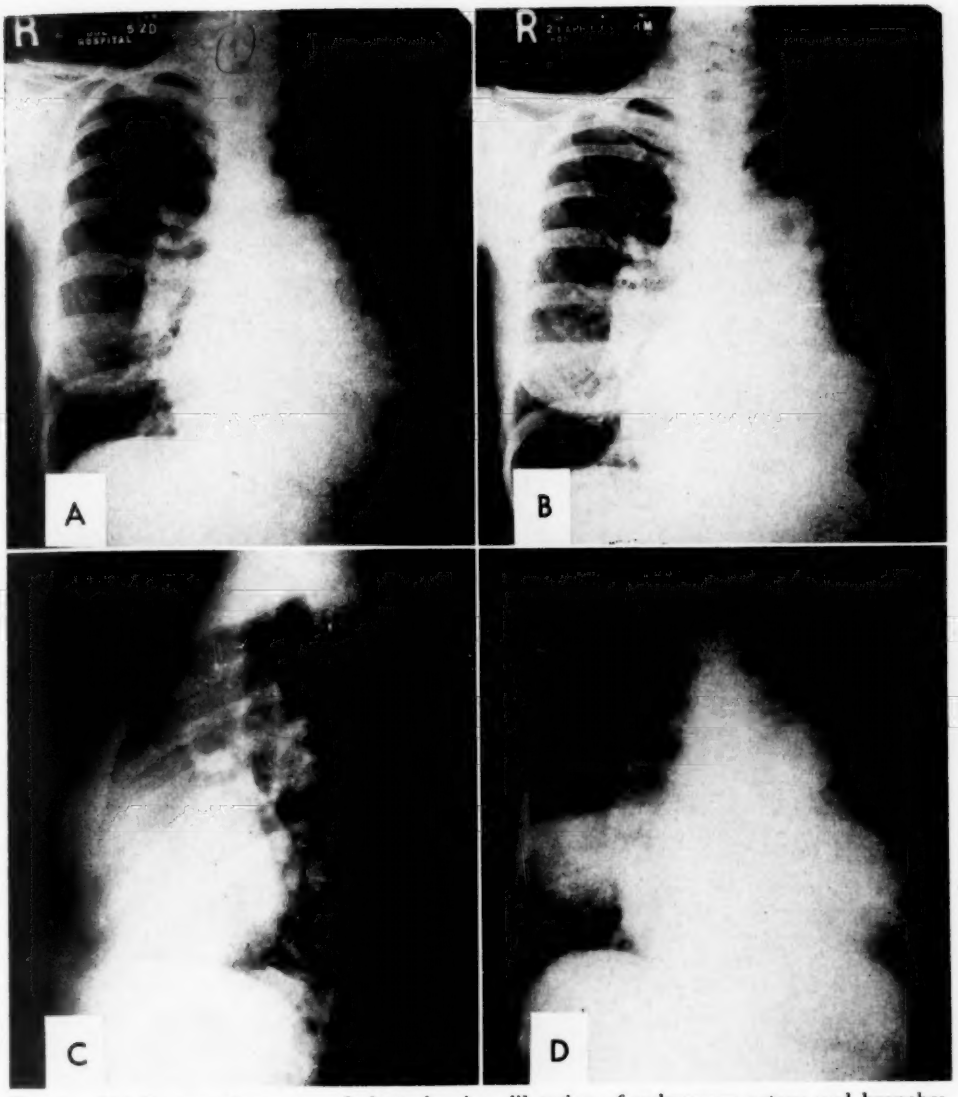

Fig. 1. (A) Preoperative x-ray of chest showing dilatation of pulmonary artery and branches. (B) and (C) Posteroanterior and left lateral films 7 months postoperatively showing aneurysm at site of ductus. (D) Film taken eight months postoperatively showing opacity in right lung due to mycotic aneurysm of a branch of the pulmonary artery.

but the shadow in the right lower lung was essentially unchanged.

Early in August, 1953, she began to cough small amounts of dark blood and on August 20, several mouthfuls of bright red blood gushed forth. Physical examination was essentially the same with no signs of consolidation in the right lower lobe. On fluoroscopy, however, the same density as before was noted in the right lung, the shape now being somewhat triangular with a sharp upper border. Barium swallow revealed no esophageal obstruction.

The possibility that the aneurysm was leaking into the bronchial tree was considered but the lesion of the right lung could not be fitted into this diagnosis. It was concluded finally that she had had a large embolus to the right lower lobe from a thrombus in the aneurysm of the ductus. She was discharged on August 30, 1953.

She continued to have occasional slight hemoptyses but was otherwise fairly well until September 17, 1953, when she was found dead on the floor in a pool of blood.

POSTMORTEM EXAMINATION

The body was that of a frail white woman showing marked pallor and distinct cyanosis of the lips, mucous membranes, ears, and finger tips. Frothy dark red blood exuded from the mouth and external nares. A healed surgical incision, 18 cm in length, was present on the left side following the line of the ninth rib. The

thoracic cage was elongated and narrow in type but symmetrical. The autopsy was limited to the examination of the thorax.

Heart and Great Vessels: The pericardial surfaces were smooth and glistening and the pericardial cavity contained a small amount of clear yellow fluid.

The heart weighed 520 Gm, was globular in outline and firm in consistency. There was little subpericardial fat. The coronary arteries showed a moderate degree of atheroma but were freely patent and normal in size and distribution. On opening the heart, marked hypertrophy of the myocardium became apparent which was particularly evident in both ventricles. The thickness of the wall of the right ventricle averaged 1.2 cm while that of the left ventricle averaged 2.4 cm. The cardiac valves were normal. No septal defects were noted and no mural thrombi were found in any of the chambers.

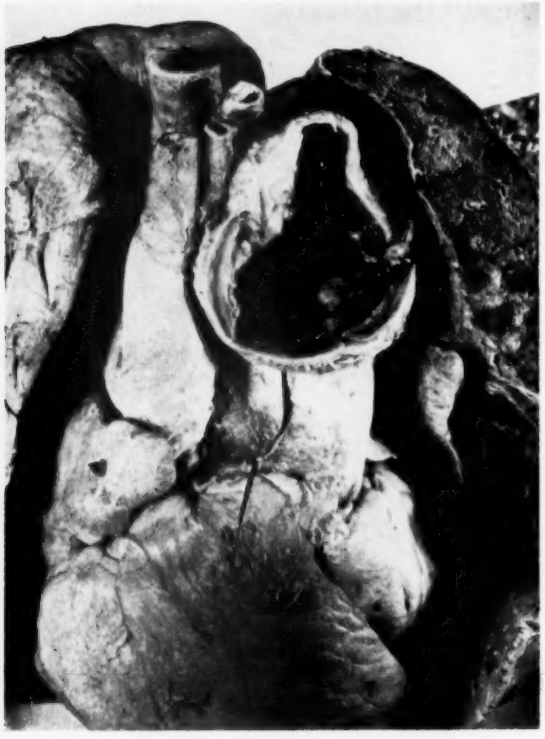

Fig. 2. Aneurysm of the ductus with the anterior half removed.

A large saccular aneurysm, measuring 5 × 4 × 4 cm, was located in the superior mediastinum. It was situated above the pulmonary artery and closely applied to the left side of the arch of the aorta (Fig. 2). Its external lining appeared to be continuous with the adventitia of both the aorta and the pulmonary artery. Its wall ranged from 0.5 to 0.7 cm in thickness and its internal lining consisted of a thick layer of dark brown laminated thrombus. Two circular sutures of heavy black silk were encountered on the postero-superior aspect of the internal surface, partly embedded in thrombus, partly protruding into the lumen of the aneurysm (Fig. 3A). The aneurysm communicated with the lumen of the pulmonary artery through a large circular opening located above the bifurcation of the vessel (Fig. 3B). Two large ragged openings located on the inferior surface of the arch of the aorta and separated from each other by a large atheromatous plaque constituted the communication between this vessel and the aneurysm (Fig. 3A).

Pleural Cavities: Numerous delicate fibrous adhesions were present in both pleural cavities, particularly on the left side in the region of the operative incision. There was almost complete obliteration of the interlobar fissures of both lungs by fibrous adhesions. The pleural cavities contained no free fluid or blood.

Lungs: The right lung weighed 1,170 Gm and was very firm, almost solid in consistency and of a dark red color. The air-passages contained large quantities of frothy blood and all branches of the pulmonary artery revealed marked atheromatous involvement. A large saccular aneurysm measuring 2.5 cm in diameter, and originating from a large branch of the pulmonary artery, was found occupying the apex of the lower lobe. It was almost completely filled by laminated thrombus of recent origin (Fig. 4), and had ruptured into an adjacent bronchus. The latter contained a large tuft of white

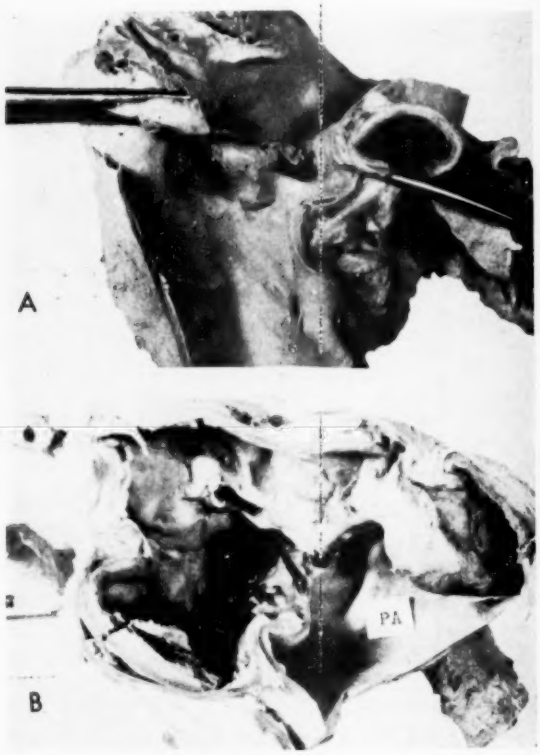

Fig. 3. (A) The two communications of the aneurysm of the ductus with the aorta. (B) The communication of the aneurysm with the pulmonary artery (PA). Two silk sutures can be seen within its lumen.

woven cotton ("umbilical tape") which appeared to have been extruded into its lumen from the aneurysm. The lung segment distal to the aneurysm was firm, atelectatic, and its air passages contained inspissated secretion but no blood. The remainder of the parenchyma of the right lung was uniformly firm and dark red.

Fig. 4. Rupture of the mycotic aneurysm of the pulmonary artery into an adjacent bronchus in which a tuft of cotton can be seen. The artery giving rise to the aneurysm is seen immediately above the bronchus.

The left lung weighed 710 Gm. Its air passages and arteries presented a similar appearance to those seen in the right lung. There was also extensive hemorrhage into the lung parenchyma, but this was less massive than that found on the right side. The examination of the remaining thoracic viscera revealed no significant findings apart from the presence of large amount of blood in the trachea.

Microscopic Examination: Microscopic examination of the wall of the large mediastinal aneurysm revealed an internal lining of laminated thrombus and a dense external layer of fibrous tissue. No muscle fibers could be recognized.

Both lungs showed a striking degree of atheromatous involvement of all large and medium sized branches of the pulmonary artery. Sections from the lower lobe of the right lung showed massive recent hemorrhage into all air passages and into large areas of lung parenchyma. One artery showed a large aneurysmal dilatation which was filled by thrombus. This thrombus was of recent origin and showed no organization. Muscle fibers as well as elastic fibrils were apparent in some portions of the aneurysmal wall while in others it consisted of fibrous tissue without remnants of the original arterial wall. At the point of rupture of the aneurysm into the adjacent bronchus, its wall had been replaced by proliferating granulation tissue heavily infiltrated by polymorphonuclear leukocytes and giant cells of the foreign body type. The lumen of the bronchus contained many large strands of colorless, refractile cotton fibers and a few fibers of black silk embedded in large amounts of purulent exudate.

Discussion

This case presents many unusual features both clinical and pathologic. The presenting symptom was the relatively rare one of hoarseness due to recurrent laryngeal nerve paralysis from pressure by a dilated tense pulmonary artery. Hoarseness is much oftener due to aortic lues or mitral stenosis than to congenital heart disease. Atrial fibrillation evidently occurred early in the course of her illness; in our experience it is uncommon in congenital heart disease except possibly in the terminal stages. The only auscultatory findings were those of pulmonary regurgitation. No murmurs due to flow through the ductus were heard at any time, presumably because of the small pressure gradient. The amount of the flow must, however, have been considerable as indicated by the difference of nearly 3 vol. % in the oxygen content of the pulmonary artery blood before and after ligation of the ductus arteriosus.

The ductus was large and difficult to mobilize and to occlude. Except for the more quiet action of her heart, the operation produced no benefit. Seven months postoperatively a large aneurysm of the ductus was found on routine examination. One month later, she developed pulmonary symptoms and was found to have a large opacity in the lower lobe of the right lung. Hemoptysis began about 11 months after operation and persisted until her death a month later from massive pulmonary hemorrhage. It was presumed that the aneurysm of the ductus had eroded into a bronchus, and also that massive embolism from thrombus in the aneurysm had occurred to the right lung, though the nature of the embolic material was not appreciated until autopsy was done.

Postmortem examination revealed that the aneurysm of the ductus had in fact not ruptured but that the fatal hemorrhage was due to the rupture into the bronchus of a mycotic aneurysm of a branch of the pulmonary artery to the right lower lobe. This mycotic aneurysm resulted from inflammatory destruction of the arterial wall as a result of embolization by cotton and silk ligature material. Although the reaction in the arterial wall was both suppurative and granulomatous, no evidence of bacterial infection was found. The lung was fixed before the

aneurysm was found, so no cultures were taken; however, bacterial colonies were not identified microscopically. The large aneurysm arising from the ductus showed sequestration of suture material into its lumen and it was doubtless from this site that the ligature material broke away and was swept to the lower lobe of the right lung.

It appears likely that the communication between the aneurysm arising from the ductus and the pulmonary artery represents the greatly enlarged pulmonary opening of the ductus. The two openings into the aorta, on the other hand, appear to lie on either side of the original ductal opening.

It is not probable that even tightly placed ligatures could fully occlude such a large and tense ductus. Continued pressure and flow through the stenosed aortic end of the ductus might then create a situation similar to that described by Holman.[12] Distal to the point of stenosis, marked turbulence of the blood stream occurs with increase in lateral pressure resulting in progressive dilatation. In the aorta, however, there is a large diversion of blood from the stenosed channel and Holman suggests that this may prevent poststenotic dilatation from occurring. Nevertheless it is difficult to offer any other explanation.

Re-establishment of the fistula following ligation only is a well-recognized complication in about 10 per cent of cases. For this reason, complete division of the ductus has been strongly advised by Gross[11] and others and is now standard practice. Technical difficulties prevented its employment in this case and resulted in a most unusual train of events. Even if the ductus could have been divided it seems unlikely that much benefit could have been derived in view of the gross hypertrophy of both ventricles and the severe sclerotic changes in the vessels of the lungs. The consensus is that most ducti should be operated upon. A number of patients older than this case have been successfully treated. Nonetheless careful consideration should be given to such unfavorable factors as the age of the patient, the probable size of the ductus, the size of the heart, and the possibility of severe pulmonary arteriosclerosis.

Summary

(1) The case of a 34-year-old woman with a large patent ductus is reported, with the unusual presenting symptom of hoarseness. Examination revealed no murmurs in the region of the ductus, the only auscultatory finding being that of pulmonary valve regurgitation.

(2) For technical reasons, only ligation of the ductus was carried out. Seven months later a large aneurysm of the ductus was discovered. One month later a mass appeared in the lower lobe of the right lung. One year postoperatively the patient died of a massive pulmonary hemorrhage.

(3) At autopsy the ligatures were found to have cut through and a large aneurysm had formed between the aorta and pulmonary artery at the site of the ductus. The fatal rupture however had not occurred at this site but was due to a mycotic aneurysm of the pulmonary artery branch to the lower lobe of the right lung.

(4) This mycotic aneurysm had formed as a result of embolization of cotton and silk ligature material from the site of the ductus to a branch of the right pulmonary artery.

Acknowledgments

We are indebted to Dr. F. A. L. Mathewson of Winnipeg and to Dr. B. W. Vale of Toronto for supplying certain clinical data.

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Unsuspected Rupture of Aortic Sinus Aneurysm into the Right Atrium

Associated Coarctation of Aorta, Bicuspid Aortic Valve, Aortic Stenosis, and Bacterial Endocarditis*

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VIRTUALLY all recent discussions and case reports describing the syndrome of rupture of an aneurysm of an aortic sinus (of Valsalva) into the right side of the heart list the typical clinical features of chest pain and dyspnea accompanied by the appearance of a loud continuous murmur of the machinery type and the peripheral signs of aortic insufficiency and tricuspid insufficiency.[1–6] Such patients commonly survive for weeks or months with evidence of congestive heart failure. Sudden death at the time of rupture is not a feature of this syndrome.

We recently encountered a patient who displayed none of the usual symptoms and signs. There were, in addition, a number of other unusual pathologic findings including a surgically repaired coarctation of the aorta which occurred proximal to the origin of the left subclavian artery, severe aortic valvular stenosis associated with a bicuspid aortic valve, and bacterial endocarditis of the aortic and mitral valves due to a group G (Lancefield) beta hemolytic streptococcus.

CASE HISTORY

R. M. (Unit No. 369766), an 18-year-old white male, was admitted to the University of Illinois Research and Educational Hospitals on May 7, 1957, and died June 4, 1957. Six weeks prior to admission he developed fever, chills, headache, malaise, and arthralgia of the left knee. His weight decreased ten pounds. He had received unknown amounts of penicillin orally and parenterally with transient improvement.

Previous History: His past history was pertinent in that an abnormality of the heart was noted in 1945 during a routine pre-school examination. He was then asymptomatic. The heart was known to be enlarged in 1946. In 1950 he was admitted to the University of Illinois Research and Educational Hospitals for diagnostic evaluation. The heart was moderately enlarged with a very loud systolic murmur and thrill in the aortic valve area. The left radial pulse was noticeably weak. Blood pressure in the right arm was 117 mm Hg systolic, 90 mm Hg diastolic; in the left arm it was 90/80, and in the right leg, not obtainable. Roentgenographic study revealed moderate left ventricular hypertrophy, marked notching of the inferior borders of the ribs which was confined to the right side of the thorax, and a prominent ascending aorta (Fig. 1). Electrocardiogram revealed incomplete left bundle branch block. Angiocardiograms demonstrated narrowing of the origin of the left subclavian artery. The diagnostic impression was coarctation of the aorta proximal to the left subclavian artery with subaortic or aortic stenosis. Resection of the coarcted area was successfully carried out in August 1950 at another hospital. There was nearly complete atresia of the aorta. The left subclavian artery was divided, leaving its proximal end separated from the aorta. After anastomosis of the aorta about 75 per cent of the normal aortic lumen was restored.

Following operation the femoral pulse was palpable. The loud aortic systolic murmur persisted, and evidence of progressive left ventricular hypertrophy was noted. The patient continued to be asymptomatic on full activity until the onset six and a half years later of the symptoms described above.

Clinical Findings: Examination on admission to the hospital (May 7, 1957) revealed a tall white male with a

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temperature of 102° F. The blood pressure in the right arm was 118/75, in the left arm 102/70, and in the left leg 108/84. The pulse rate was 95 per minute and regular. The left radial pulse was weak. There were several petechiae on the soft palate and conjunctiva. There was no clubbing. Splenomegaly was noted by some observers. The cardiac apex was prominent at the left anterior axillary line. There was a grade 5 aortic systolic murmur, with thrill, transmitted into the neck and over the entire precordium. No diastolic murmurs were heard. A prominent third sound was audible in the apical area. Femoral pulses were faint but palpable.

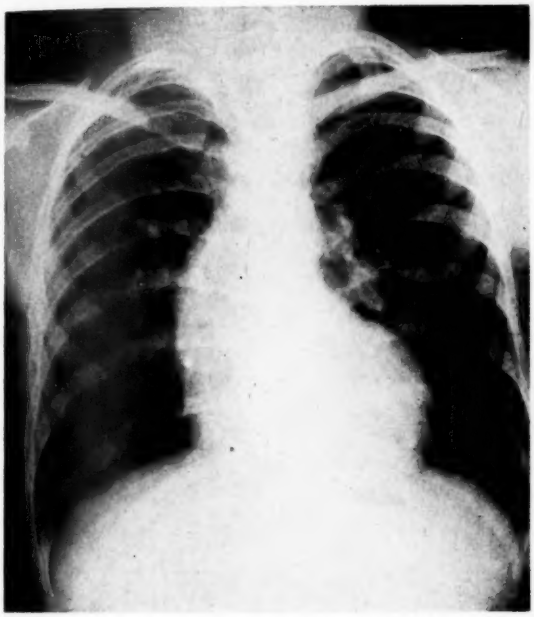

Fig. 1. Chest roentgenogram taken June 26, 1950, seven years before bacterial endocarditis and two months before repair of coarctation of the aorta. Note rib notching only on the right side, enlarged ascending aorta and prominent left ventricle.

Hemoglobin measured 11.2 g/100 ml, leukocytes numbered 13,850/cu mm and the corrected Wintrobe sedimentation rate was 14 mm/hour. Urinalysis was negative. Chest roentgenogram revealed left ventricular hypertrophy which had increased since 1955. Electrocardiogram showed first degree A-V block (P-R 0.38 sec), not present in 1955, and incomplete left bundle branch block.

Clinical Course: Because of findings strongly suggestive of bacterial endocarditis, penicillin and streptomycin were started on the second hospital day in doses of 600,000 units and 0.5 g, respectively, intramuscularly every six hours. Diagnoses of aortic stenosis and surgically repaired coarctation of the aorta were also made. Each of the first five consecutive blood cultures revealed growth of a beta hemolytic streptococcus, group G. This organism was inhibited by 1.0 unit of penicillin/ml and 16 μg of streptomycin/ml (tube dilution method).

Because the patient remained febrile and the streptococcus was only moderately sensitive to penicillin, the penicillin dosage was raised to 20 million units daily by continuous intravenous infusion on the fourth hospital day and continued at this level throughout the remainder of the patient's life. Streptomycin dosage was reduced to 0.5 g every 12 hours on the 15th hospital day and continued until the patient died on the 28th day of hospitalization.

After two weeks of penicillin-streptomycin therapy, the patient became febrile and remained so until a few hours before death. Eleven blood cultures were obtained after beginning antibiotic treatment and all were negative for pathogens. The patient continued to feel quite well until the 16th hospital day, when anorexia and periumbilical pain appeared. The pain later was localized to the right lower quadrant of the abdomen. A diagnosis of probable subacute appendicitis was made and surgical consultation was obtained. The patient was carefully observed, and abdominal symptoms largely subsided in five days. The white cell count returned to normal values. After five more days of well being, the pulse rate rose rather sharply from 80 to 110/min and sharp right lower quadrant abdominal pain recurred, accompanied by repeated vomiting. On digital examination of the rectum, a tender fluctuant bulge was felt in the rectovesical pouch, with pain referred to the right lower abdomen. The leukocyte count rose to 13,000/cu mm and the rectal temperature gradually climbed to 101.6° F. The majority of the staff believed that the patient had an appendiceal abscess, probably with recent rupture and pelvic peritonitis. The patient died unexpectedly a few hours later, before laparotomy could be performed.

An electrocardiogram on the day before death, when tachycardia appeared, revealed a P-R interval of 0.28 sec, a sinus tachycardia of 108 beats/min, and incomplete left bundle branch block. Blood pressure at this time was normal but a few hours before death the blood pressure in the right arm was recorded as 130 systolic and 0 to 40 diastolic. There was no change in the systolic murmur. Just before death the heart rate became rapid and irregular followed by pulselessness and apnea. Emergency thoracotomy revealed ventricular fibrillation. Electric shock, cardiac massage, intracardiac epinephrine, and calcium gluconate were tried to no avail.

Autopsy Findings

Necropsy* revealed an adult type of coarctation of the aorta treated seven years previously by surgical excision and end to end anastomosis. There was some recurrent stenosis at the operative site, the aorta decreasing

* Necropsy was performed by George Scaravelli, M.D., to whom the authors are indebted for assistance in reviewing the pathologic findings.

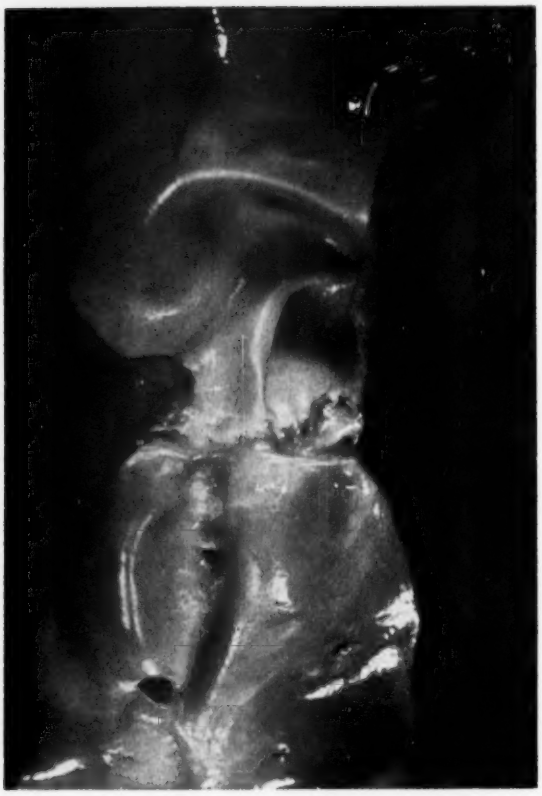

Fig. 2. The opened thoracic aorta is shown, revealing the previous end-to-end anastomosis after resection of the coarcted area. Note that the orifices of the right intercostal arteries are several times larger than those of the left.

in circumference from 5.6 to 2.3 cm at the level of narrowing. Below the stenosed area the aorta measured 4.5 cm in circumference. The right internal mammary artery was considerably enlarged and about three times the diameter of the left. The intercostal arteries on the right side were considerably larger than those on the left (Fig. 2). The left subclavian artery had been ligated at operation and did not directly join either the aorta or the left common carotid artery.

Marked left ventricular hypertrophy, moderate right ventricular hypertrophy and marked right ventricular dilatation were present. The heart weighed 760 g. Hepatic congestion (1,720 g) and definite splenomegaly (530 g) were found. Subacute appendicitis was noted but there was no evidence of appendiceal abscess or perforation.

A bicuspid aortic valve with severe aortic stenosis was found. The aortic valve admitted the tip of a small finger and when opened measured 4.3 cm in circumference. The cusps were completely rigid. Changes consistent with healing bacterial endocarditis were seen, including gross valvular vegetations. There was extension of the infection to the mitral valve and on microscopic examination calcification was visible in both aortic and mitral valves.

An unsuspected finding was a mycotic aneurysm of the aortic sinuses (Fig. 3). This aneurysm arose from the right and posterior (noncoronary) aortic sinuses which were fused into one large pocket. The left coronary sinus was smaller than usual. The aneurysm was large enough to admit a thumb easily. There were two areas of perforation originating from this aneurysm. One communicated through an aortic valve cusp into the left ventricle with an opening measuring 0.7 cm

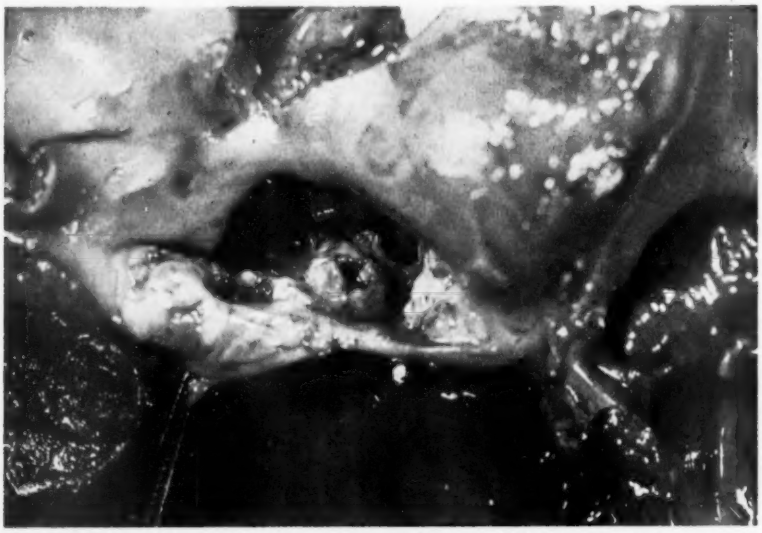

Fig. 3. Interior view of the heart with the left ventricle below and the ascending aorta above. The aneurysm of the right and posterior aortic sinuses is shown. One area of perforation of the aneurysm through the aortic cusp into the left ventricular chamber is easily visible. The point of rupture into the right atrium lies deeper and is not well seen here.

in diameter. Grossly visible vegetations were noted at the inferior opening. The other perforation extended into the right atrium through a firm conical protrusion with an opening 0.5 cm at the tip. The heart's blood obtained postmortem revealed no growth.

The major pathologic diagnoses, therefore, were (1) coarctation of the aorta, surgically excised, with recurrent stenosis at the site of operation; (2) bicuspid aortic valve with aortic valvular stenosis; (3) left and right ventricular hypertrophy; (4) bacterial endocarditis, healing, involving the aortic and mitral valves; (5) mycotic aneurysm of the right and noncoronary sinuses of Valsalva with perforation and rupture into the right atrium and into the left ventricle.

Discussion

Coarctation of the Aorta, Bicuspid Aortic Valve, and Aortic Stenosis: This case presents a number of unusual features. The association of aortic valvular stenosis with coarctation of the aorta was recently discussed by Smith and Matthews.[7] They reviewed the original reports of Abbott's series[8] of 200 cases of coarctation and found aortic valvular stenosis in 6.5 per cent. Of 27 necropsied cases with this combination, 20 had a bicuspid aortic valve. The great majority of the bicuspid valves were felt to be of congenital origin and it was concluded that degeneration in a congenital bicuspid aortic valve can lead to aortic stenosis because of the inherently defective valvular structure and the higher pressure to which it is subjected in coarctation of the aorta. The frequency of bicuspid aortic valves in coarctation is well known, having been found in 25 per cent of 200 cases[8] and in 42 per cent of 104 cases.[9] Since a bicuspid aortic valve was associated with the combination of coarctation and aortic valvular stenosis in 74 per cent of 27 reported cases,[7] it would seem to be two or three times as common there as in a general series of cases of coarctation of the aorta.

Aortic stenosis is to be suspected in cases of coarctation where there is well marked left ventricular hypertrophy by radiologic and electrocardiographic study.[10] It is interesting that although femoral pulses appeared and were maintained after surgical repair of the coarctation, left ventricular hypertrophy progressed relentlessly, doubtless due to the aortic stenosis. At necropsy seven years after the operation there was considerable re-stenosis in the area of coarctation. At no time before or after surgery was a significant elevation of blood pressure noted in the right arm. Blood pressures were easily obtained from the legs after operation but were always lower than in the right arm.

Coarctation of the aorta proximal to the origin of the left subclavian artery (presubclavian coarctation) was diagnosed preoperatively in this patient because of the weaker left radial pulse, lower blood pressure in the left arm and the finding of notching of the ribs only on the right side.[10,11] This diagnosis was confirmed at surgery and well illustrated on postmortem examination by internal mammary and intercostal arteries which were strikingly larger on the right as compared to those on the left. Abbott found the coarctation at or above the origin of the left subclavian artery in 7 of 200 cases.[8]

Bacterial Endocarditis: The complication of bacterial endocarditis is a dangerous threat to patients with coarctation, accounting for about one-fifth of the deaths.[8,9] The risk is particularly great where a bicuspid aortic valve is associated, since the vegetations commonly first appear there. Reifenstein *et al.*[9] found a bicuspid aortic valve in 71 per cent of the cases of coarctation in which bacterial endocarditis involved the valve itself.

The diagnosis of bacterial endocarditis was easy in this case and was promptly confirmed by positive blood cultures. As all too often happens, this patient's infection was controlled by antibiotic therapy, as shown by return of his temperature to normal and persistently negative blood cultures after treatment was started and at necropsy, but death was due to an irreversible complication—in this case rupture of an aneurysm of the sinus of Valsalva into the right atrium. Endocarditis due to the group G beta hemolytic streptococcus is quite uncommon but this organism has been previously isolated in cases of the disease. In the case reported here, the minimal inhibitory concentration of penicillin was 1.0 unit per ml. The group G streptococcus obtained from the patient of Santos-Buch *et al.*[12] required only 0.049 unit of penicillin per ml for inhibition.

Aneurysm of Aortic Sinuses

Jones and Langley[2] have discussed the

clinical significance of aortic sinus aneurysms. Including their four cases they collected a verified series of 25 congenital and 22 acquired sinus aneurysms. The cases consisted of both ruptured and unruptured aneurysms. The essential pathology is a separation of the aortic media from the heart. Congenital sinus aneurysms were associated with other congenital cardiovascular malformation in 23 of 25 cases. Twenty-one of the 25 aneurysms revealed a communication with the heart or great vessels, 13 with the right ventricle, 6 with the right atrium, and one each with the left ventricle and pulmonary artery. Twenty of the 25 aneurysms arose from the right coronary sinus and five from the posterior (noncoronary) sinus. Six of the 25 patients with congenital aneurysms died of bacterial endocarditis. Congenital unruptured aortic sinus aneurysms are, like bicuspid aortic valves, one of the silent lesions to be suspected when bacterial endocarditis develops in a heart apparently previously healthy.

Perforation of Aortic Sinus Aneurysm into Right Atrium: In recent years, a number of authors have suggested that one should expect to diagnose antemortem most cases of rupture of an aneurysm of the sinus of Valsalva into the right atrium. From their case reports a fairly consistent clinical picture emerges. At the time of their report in 1955, Oram and East[3] found only 23 published cases, including their two, of rupture of aneurysms of the sinus of Valsalva into the right side of the heart in which the patient lived long enough to develop symptoms and signs of the condition. These patients lived from 7 days to 17 years (usually weeks to months) after onset of symptoms or signs. The etiology of the aneurysm was considered to be congenital in 14, bacterial endocarditis in 4, syphilis in 3, and uncertain in 2. All patients were 20 years of age or older. Even in congenital aneurysms, rupture apparently did not occur until early adult life. The ruptured aneurysm was usually found in the right coronary sinus (14 cases), occasionally in the noncoronary sinus (7 cases) and infrequently in the left sinus (2 cases). Edwards and Burchell[5] point out that rupture of an aneurysm above the left aortic cusp is unlikely to involve the right side of the heart because of the anatomic relationships and suggest that the last two aneurysms reviewed by Oram and East may have arisen from the posterior (noncoronary) sinus. The interpretation of these case reports was difficult because of varying terminology.

Clinical Features: The typical clinical picture of rupture into the right atrium or right ventricle is ushered in by the sudden onset of severe thoracic or epigastric pain, weakness and dyspnea.[1–4,6] These symptoms may subside in a few hours to be followed by a latent period of a few days. Congestive heart failure soon appears with ankle edema, orthopnea, and cough. Cyanosis may or may not be present. At the onset of pain, a continuous murmur, usually with a palpable thrill, is found over the mid-precordium. Such a murmur was noted in 21 of 23 cases.[3] The left-to-right shunt commonly produces peripheral signs of aortic insufficiency, i.e., low diastolic pressure, Corrigan pulse, capillary pulsation, and pistol shot sounds over arteries. The pulmonic second sound is often accentuated. Peripheral signs of the type seen in tricuspid insufficiency were also present in 10 of the 23 cases collected by Oram and East,[3] including systolic pulsations in the cervical veins and an enlarged tender pulsating liver. The heart is moderately to severely enlarged. The electrocardiogram is nearly always abnormal[3] and usually shows evidence of right axis deviation and occasionally evidence of A-V block.[2,3,6,13] Atrial fibrillation may occur. Chest radiographs show cardiomegaly with or without pleural effusion. An enlarged right atrium may be noted.

Diagnosis: The sudden appearance of this syndrome in an adult who was previously healthy or who has bacterial endocarditis or syphilis should suggest the diagnosis of rupture of an aneurysm of the sinus of Valsalva into the right heart. It should be remembered that bacterial endocarditis may occur as a complication after rupture of a congenital aneurysm while in other instances the infectious process is the cause of rupture. Of course, rupture may also occur into the pulmonary artery, superior vena cava or elsewhere, usually with somewhat different findings.[1] Cardiac catheterization is helpful in assessing the magnitude of the left-

to-right shunt and its localization. Confirmation is obtained by thoracic aortography as illustrated by Morrow *et al.*[6] Until the advent of recent advances in thoracic surgery these patients could be treated only with rest, digitalis, diuretics, low sodium intake, and other measures employed for congestive heart failure. Morrow and associates[6] recently reported successful surgical repair of a ruptured aneurysm of the sinus of Valsalva, using a sponge prosthesis introduced via the aorta during a brief period of occlusion of inflow. Postoperative catheterization data indicated complete closure of the fistula, and the heart decreased markedly in size.

In the case presented here there was no real evidence on which to base a diagnosis of ruptured aneurysm of the sinus of Valsalva. The tachycardia (110–120/min) noted on the day before death was not accompanied by any change in blood pressure and no diastolic murmur was ever heard. There was no chest pain. The electrocardiogram revealed first degree A-V block present on each of the four tracings taken during hospitalization. The last previous tracing two years before revealed a P-R interval of 0.19 sec. The lengthening of the P-R interval noted here was attributed to progression of pre-existing heart disease although in retrospect the ruptured aneurysm may have played a role. The widened pulse pressure noted a few hours before death was not present the previous day. While an important feature of the syndrome, it is more often due to other causes and did not suggest the diagnosis here.

Symptoms and signs of appendicitis were the center of attention for the last 11 days of the patient's life. Increasing tenderness, a rise in white cell count and temperature and an apparent pelvic mass a few hours before death led to the suspicion of appendiceal rupture. While unequivocal subacute appendicitis was found at necropsy, there was no perforation. It seems unlikely that this process could be related to the bacterial endocarditis. Appendicitis did not appear to be the cause of death, but almost certainly was the cause of the abdominal symptoms and signs.

Summary

A case is reported of an 18-year-old male with presubclavian coarctation of the aorta repaired seven years previously who developed bacterial endocarditis due to a group G beta hemolytic streptococcus. Signs of aortic stenosis were noted before and during the endocarditis and were accompanied by left ventricular hypertrophy which had progressed since the repair of the coarctation. The infection was well controlled by penicillin-streptomycin therapy when the patient developed appendicitis. Symptoms of the latter improved and then suddenly worsened a week later. Appendiceal rupture was suspected but the patient died suddenly before surgery could be performed.

Necropsy revealed recurrent stenosis at the site of the surgical anastomosis for coarctation of the aorta, aortic valvular stenosis developing on a congenitally bicuspid valve, and subacute appendicitis. An unsuspected finding was a rupture of a mycotic aneurysm of the sinus of Valsalva into the right atrium. Pertinent articles pertaining to the unusual features of this case are briefly reviewed.

Addendum

Since this report was submitted for publication, a Symposium on Unusual Manifestations of Aortic Stenosis has appeared (*Proc. Staff Meet. Mayo Clin.* 33: 209, 1958).

Acknowledgment

The authors are indebted to Dr. E. H. Friedman for many of the detailed observations made in this case.

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The Electrocardiogram in Hyperparathyroidism*

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THE ELECTROCARDIOGRAPHIC changes accompanying hyperparathyroidism have received scant attention. We have been able to find only one previously published case documented with 12-lead electrocardiograms taken before and after parathyroidectomy.[1] Rarely, some of the changes have been recorded in fewer leads.[2–5] As the characteristic pattern may be of diagnostic value in a reversible syndrome, it seems worth while to present a further example with full tracings.

CASE HISTORY

A 53-year-old white man was admitted to the Mercy Hospital with a fracture of the right femur resulting from only modest trauma. He gave a history of persistent dyspeptic symptoms for 25 years and of having passed several small kidney stones 15 years previously. For many years he had suffered from polyuria, polydipsia, and constipation. Most of his life he had consumed about a quart of milk daily. He had noted two lumps in his neck for about 12 years and on examination two firm nodules were visible and palpable in the region of the lateral lobes of the thyroid. X-rays of the thorax and long bones revealed classic findings of osteitis fibrosa cystica with a fracture through a large cyst in the right femur. Serum calcium levels ranged between 11.6 and 15.0 mg/100 ml, serum phosphorus between 3.6 and 6.0 mg/100 ml, and alkaline phosphatase between 12 and 15 Bodansky units. The hematocrit was 33 per cent and blood urea nitrogen 76 mg/100 ml.

On his 12th hospital day the tumors in the neck were removed and proved histologically to be parathyroid adenomas. Postoperatively, serum calcium levels fell to normal (the lowest level obtained was 8.3 mg/100 ml) and the uremia and anemia improved. The dyspeptic symptoms, polydipsia, polyuria, and constipation have not recurred since surgery.

DISCUSSION OF ELECTROCARDIOGRAMS

Preoperative Record: The tracing taken before parathyroidectomy (Fig. 1A) shows striking similarities in form and measurement to that published by Bradlow and Segal.[1] The pattern of a virtually absent S-T segment and precocious apex of the T wave with slow descending limb (as seen in V_2-V_4) is one that immediately catches the eye. Unnatural flattening, rounding, or notching of the T wave is to be seen in other leads. The single most measurable deviation from the normal is the shortening of the Q-aT interval.† From the data supplied by Lepeschkin,[6] the range of normal for the Q-aT interval in a male at a rate of 80–90 is 0.24 to 0.29 sec, whereas in Figure 1A this interval measures only 0.19 sec. At the time of this tracing the serum calcium was 15 mg, phosphorus 4.5 mg, and urea nitrogen 76 mg/100 ml; serum sodium was 135 meq, chloride 98.4 meq, and potassium 3.32 meq per liter.

Postoperative Record: A more recent record (Fig. 1B) shows complete restoration to normal.

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† Measured from beginning of QRS to *apex* of T wave in whichever lead shows the tallest monophasic T wave.[6]

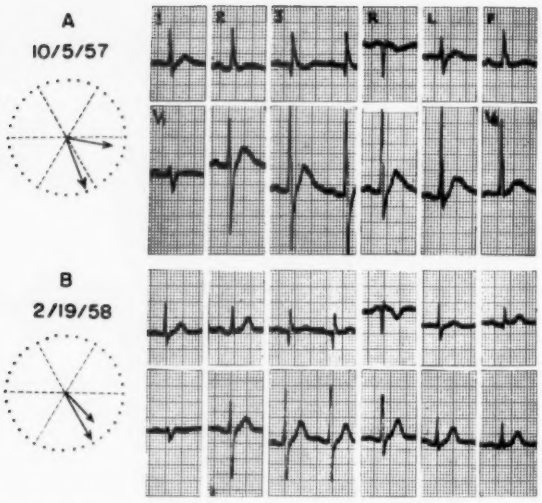

Fig. 1 (A). Record taken before parathyroidectomy. Note virtual absence of ST segment, early peak of T wave and relatively gradual downslope of descending limb of T wave. Q-aT interval is 0.19 sec (normal 0.24–0.29 sec). T wave axis in frontal plane is +15°.

(B) Record taken after recovery. Note normal contour of ST-T segment. Q-aT interval is 0.22 sec (normal 0.21–0.26 sec). T wave axis has shifted to the right and is now +45°.

The contour of the T wave is now within normal limits and, despite the faster rate, the Q-aT interval has increased to 0.22 sec (normal for rate of 100–110 is 0.21 to 0.26 sec). At this time the serum calcium was 10.7 mg, phosphorus 2.6 mg, and urea nitrogen 32 mg/100 ml; serum sodium was 140.7 meq, chloride 103.5 meq, and potassium 3.8 meq/*l*.

It is worth noting that simultaneously with restoration of the ST-T contour, the T wave axis in the frontal plane shifted rightward, from +15° before surgery to +45° after recovery. An almost identical shift in T wave axis is to be seen in the tracings published by Bradlow and Segal.[1] This tendency was previously noted by Kellogg and Kerr,[3] who observed that negative T waves in lead 3 became upright when the hyperparathyroidism was cured.

Prolongation of the P-R interval has also been observed in hyperparathyroidism[3,4] but was not noted in our case.

Comment

Too few electrocardiograms are available for study to determine whether there are consistent differences between the pattern of hyperparathyroidism and that of hypercalcemia from other causes. One may assume, however, that the increased concentration of calcium in hyperparathyroidism plays a role, and perhaps the major role, in producing the observed ST-T changes and, when present, the P-R prolongation as well; for it is known that hypercalcemia shortens systole and also enhances vagal action.[7]

Several authors have drawn attention to shortening of the Q-Tc interval as a characteristic of hypercalcemia, including the hypercalcemia of hyperparathyroidism.[1–3,8] Others have commented on the unreliability of the Q-Tc interval as an index of hypercalcemia,[4,9] and measurement of the S-T segment has been preferred.[9] The Q-T interval, however, is notoriously difficult to measure with accuracy and the S-T segment is hardly less so. In our opinion both these measurements are inferior to, because less accurate than, the Q-aT interval. In our tracings (Fig. 1A), for example, it is impossible to determine the end of the T wave with accuracy or to make a true estimate of the duration of the S-T segment—which indeed is virtually absent. On the other hand the Q-aT interval is readily and accurately measured and affords a convenient means of following progress in serial tracings.

Summary

The electrocardiographic changes in a case of hyperparathyroidism, before and after parathyroidectomy, are illustrated and briefly discussed. The shortened Q-aT interval is confirmed as a readily measured index of shortened systole, characteristic of hypercalcemia.

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Progress Notes in Cardiology

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Hydrochlorothiazide

THE SUCCESSFUL USE of chlorothiazide (Diuril, Merck Sharp & Dohme) in the treatment of congestive heart failure and hypertension has stimulated search for more potent compounds. One of the more promising to be synthesized is hydrochlorothiazide (Esidrix, Ciba; Hydrodiuril, Merck Sharp & Dohme). Two clinical reports have appeared in recent issues of this Journal (MOYER, FUCHS, IRIE, and BODI: Vol. III, January 1959, p. 113; BREST and LIKOFF: Vol. III, February 1959, p. 144).

Hydrochlorothiazide appears to be as much as ten or more times potent than chlorothiazide. It markedly increases the renal excretion of water, sodium, and chloride, and, to a lesser extent, potassium. Hypochloremia after its use is a common finding. Side effects to date have been mild; namely, nausea, anorexia, and weakness. The maximal effective dose has not yet been determined. As little as 50 mg two or three times a day has been used, and as much as 500 mg twice a day. At present, the drug is available only for investigative purposes.

Brachial Arteritis or Aortic Arch Arteritis (Pulseless Disease)

NUMEROUS REPORTS from Japan, North European countries, and the United States have brought attention to a new clinical syndrome called "pulseless" or "Takayasu" disease, and more recently "aortic arch arteritis" or "brachial arteritis." The disease is ubiquitous, because cases were also noted in Germany, China, England, Roumania, Greece, Switzerland, Spain, Hungary, and France. Most of the cases described occurred in female children and young women between the ages of 9 and 45 years; in a few instances the disorder was also observed in young men. An interesting review by Dr. Bohdan J. Koszewski recently appeared (*Angiology* 9: 180, 1958).

The beginning of the disease is insidious and the clinical picture varies greatly. It consists of vascular, cardiac, trophic, cerebral, and ocular symptoms. The most characteristic vascular sign is the absence of arterial pulsation in neck, head, and arms due to arterial thrombosis and strong pulses in the legs, comparable to "reversed coarctation." The brachial arteries and the thyrocervical trunk remain intact, building a rich network of anastomoses around the neck and shoulders and supplying the brain with blood through hypertrophic vertebral arteries. This results in vascular thrills in the neck, palpable pulsations on the chest, and crenation of the rib margins. The aorta is also involved, but anginal symptoms are rare and coronary thrombosis occurs only in terminal stages. Trophic changes may be seen about the head such as loss of teeth and hair, ulcers on the lips or the tip of the nose, and perforation of the nasal septum. Organic skin changes in the arms are absent, but diminished blood supply brings easy fatigability as well as a feeling of coolness in hands and fingers. Cerebral phenomena consist of dull headache, giddiness, fainting spells, mental impairment, convulsive disorders, and usually terminal hemiplegia. Hypersensitive carotid sinuses are common. The ocular disturbances cause photopsia and blurring of vision on exertion. Diagnostically important are the eyeground changes,

described by Takayasu, consisting of a crownlike assortment of dilated vessels around the optic disc due to multiple peripapillary arteriovenous anastomoses. Advanced stages are marked by cataracts, atrophy of the retina and iris, and terminal blindness. The disease is, as a rule, accompanied by less specific but nevertheless important general symptoms, such as a low-grade fever, loss of weight, anemia, leukocytosis, and high erythrocyte sedimentation rate.

The primary lesion consists of an acute, almost phlegmonous periarteritis. The cellular infiltration is quite extensive and reaches internal layers, causing necrosis of the media and intra-arterial thrombosis. Later stages are characterized by fibroblastic hypertrophy of adventitia and media with lymphocytic and plasma cellular infiltration. In classical cases the arteritis is restricted to the vessels derived from the original brachial arteries, i.e. the large elastic arteries of the aortic arch, as well as the thoracic aorta. The vessels distal to the diseased area are free from inflammation or thrombosis. The abdominal aorta and its branches are also unchanged. This segmental distribution is conspicuous and justifies the denomination as "brachial arteritis."

Brachial arteritis should be differentiated from similar syndromes. Absent or diminished radial and/or cervical pulses can be seen in congenital anomalies of the arch, aortic aneurysms, chronic dissection of the aorta, embolism, auricular ball thrombus, atheromatosis with and without thrombosis, syphilitic arteritis, thromboangiitis obliterans, periarteritis nodosa, temporal arteritis, thrombophilia, and lupus erythematosus. However, the characteristic vascular, cardiac, trophic, cerebral, ocular, and general symptoms permit its differentiation from those diseases. The cause of the brachial arteritis is unknown. Prognosis is grave, as most patients die before reaching the fourth decade. No effective treatment is available, although the preliminary results with combined steroid and anticoagulant therapy are encouraging.

Cardiac Resuscitation

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Historical Notes on Cardiorespiratory Resuscitation

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FROM time immemorial man has succumbed to some form of asphyxia. It is reasonable to assume that down through the ages before written history there have been numerous and diversified attempts at revival, occasionally successful. In this twentieth century the resuscitation problem still exists.

Asphyxial episodes have been common to man since antiquity. "Asphyxia" in the original Greek meant a stoppage of the pulse (cardiac cessation). Aristotle made the sagacious observation that breathing was difficult on Mount Olympus, because the air was too thin. Some of the causes of fatal asphyxia then, as now, were drowning, strangulation, suffocation by smoke and noxious gases, asphyxia neonatorum, lightning, electrocution, smothering, overdosage of drugs and alcohol, aspiration of vomitus, diseases, etc. (see AM. J. CARDIOL., Vol. 2, 1958).

Somewhat cynically one might say that in the final analysis, death always results in asphyxia, but the test is in the key word *cause:* Was death caused by asphyxia?

Respiratory Resuscitation: Mouth-to-mouth respiration was the method of choice in the treatment of asphyxia prior to the year 1530. It was practiced widely and is described in the Bible, II Kings, Chapter 4, Verse 34. Following the sixteenth century, other forms of artificial respiration began to be thought more suitable, as this act was considered vulgar. However, it was practiced by peasant midwives until Louis Pasteur's discoveries dealt it an almost lethal blow.†

European surgeons performed tracheotomies as early as the twelfth and thirteenth centuries. In 1530 Paracelsus introduced the common fireside bellows as a means of introducing air into the lungs. Smellie in 1763 developed the principle of mouth-to-mouth insufflation by the medium of a flexible tube. This tube was inserted into the throat and trachea, and a glass bulb in its middle collected mucus when suction was applied. This tube has its counterpart today, two centuries later. Introduced by direct vision, it is our best method of resuscitating the flaccid patient.

Serious attempts to resuscitate the newborn date back to the middle of the eighteenth century. During the first half of the nineteenth century, great interest in this particular field is noted. However, it seems that none of the methods of that period, other than mouth-to-mouth insufflation, has stood the test of time. The concept introduced by Little, in 1842, that many physical disabilities in children (cerebral palsy) are attributable to asphyxia in the newborn had to be learned all over again.

Man's persistent dream of overcoming pain was partially realized with the successful introduction of ether and chloroform anesthesia in 1846 and 1847, respectively. Shortly thereafter, obscure incidents of collapse under anesthesia occurred that today would be called cardiac arrests.

The era of modern surgery began with the successful administration of these specific chemical gases (ether and chloroform). However, it

* President, National Resuscitation Society.

† Although the hazard of contamination remains, new devices bypass or minimize it.

soon became apparent to the pioneers in anesthesia that great care had to be exercised in the administration of these useful stupefying and pain-relieving gases if their inherent benefits were to be realized.

The intensity of the opposition to chloroform and anesthesia in general was particularly great in the British Isles. We are familiar with the fact that Queen Victoria was given chloroform during her confinement in 1853. It is interesting to reflect the responsibility assumed by John Snow and James Simpson and also to reflect that if tragedy on this historic occasion had resulted, would it have impeded the progress of anesthesia 25 years or more? Overnight James Simpson's reputation as a charlatan was exchanged for a baronetcy. Overnight the medical profession of England accepted anesthesia.

Cardiac Massage: In European laboratories physiologists reported that in animals hearts which had ceased to beat could be made to resume a normal beat after a period of squeezing their ventricles. Schiff in 1874 was one of the first to record experiments in which he carried out successful heart massage on anesthetized animals whose hearts had been quiescent up to $11^1/_2$ minutes.

At this time not all resuscitation endeavors were confined to the laboratory. In 1889 Niehaus of Berne was apparently the first to attempt resuscitation of the human heart by manual massage. Maag, in 1900, had the first partial success. His patient survived 11 hours after the restoration of the heart beat. Starling and Lane[1] reported the first successful cardiac resuscitation in 1902. Arbuthnot Lane performed an abdominal operation on a 65-year-old male. The heart unexpectedly stopped. Artificial respiration was instituted. Lane massaged the heart via the subdiaphragmatic approach and soon a satisfactory pulse was obtained. Inglesburd in 1903 reported that two years previously he had successfully resuscitated a human patient in the operating room. Hamilton Bailey made many outstanding contributions to this field. Shortly after the turn of this century, Ringer, Kuliabo, and Sollman showed that the excised heart could be made to beat again after fairly long periods of quiescence.

In this country, a considerable amount of experimental and clinical investigation was done in Cleveland, Ohio. Sollman,[2] in 1905, stated that one of the best stimulants to an arrested heart in the laboratory was adequate filling of the chambers of the heart with resultant stretching of the muscle fibers and coronary vessels. The inauguration of the beat was more dependent upon the physical factor of the increased pressure in the coronary arteries than upon the quality of the fluid producing such pressure. Crile and Dolley[3] published their laboratory work on the resuscitation of dogs in 1906. It is interesting that their conclusions are so notable today. They found no difficulty in reviving the asphyxiated heart with perfusion or massage.

Crile, in 1904, reported the successful resuscitation of a 12-year-old girl in the operating room following the perfusion under pressure of an adrenalin solution into the brachial artery. He personally followed this girl's career for many years. A queer lack of knowledge or acceptance has prevailed in medical circles concerning the following observation by Crile 50 years ago: "In regard to resuscitation of the body as a whole, the fact has not been sufficiently appreciated that the greatest and most essential difficulty is to overcome the anemia of the brain, rather than the heart."

Cardiac Defibrillation: By clinical and laboratory observation it became apparent that successful restoration of the heart beat could be accomplished when the heart was found in a quiescent state or asystole. Many times it was found in a quivering or fibrillating state, and little or nothing could be done to induce the organ to return to a coordinated beat. Could it be that this fact or statement was a stumbling block which retarded progress in this field? However, two French investigators, Batelli and Prevost in 1899 successfully brought dogs' hearts out of ventricular fibrillation by application of strong alternating electrical currents. Their work attracted little attention.

Some twenty-five to thirty years later, Hooker, Kouwenhoven, Langworthy, and Wiggers reported similar achievements from their laboratories while experimenting with the dog's heart. Hooker[4] and other investigators had

been successful in defibrillation by arterial perfusion with the proper combination of calcium, sodium, and potassium ions. This has had very little practical application at the moment of an emergency.

Early in 1933 Claude Beck embarked upon his monumental work of developing a valuable surgical procedure to combat nature's foremost killer, coronary insufficiency. Rather frequently after weeks and months of labor, upon tightening down the small clamp on the coronary arteries the dog's heart would fibrillate. Beck thus became engrossed in the subject of resuscitation and decided to do something about it, if only to salvage some of the weeks of labor spent upon the laboratory animals. Thus resuscitation was introduced into the coronary research problem. Twenty-two years later it was introduced into the clinical coronary problem by Beck.[8] The results were definitely improved when Beck and Mautz[5] introduced procaine into the procedure to reduce the surface irritability of the heart and to decrease the hyperirritability of the myocardium. Unbeknown to them, François-Franck had done somewhat similar experiments on animals with cocaine in the 1890's.

The first authenticated successful case of defibrillation of the human heart was carried out by Beck[6] in 1947. After 75 minutes of cardiac massage and a series of electrical shocks the heart returned to a coordinated beat. The patient, then a young boy, has led a normal life since his convalescence.

A practical suction cup electrode defibrillator was developed by Rand and Beck[7] after considerable experimentation in 1949. From 1902 until this time there were some successful cardiac resuscitations occurring in operating rooms, but the reports were few and scattered.

Educational Programs in Respirocardiac Resuscitation: The concept that asphyxia constituted a major medical problem was confirmed by a group of doctors in 1933. Among them were Paluel Flagg, Chevalier Jackson, Yandell Henderson, and Alexis Carrel. A new society was formed and called the Society for the Prevention of Asphyxial Deaths. Through the untiring efforts of Flagg this society has filled a certain vacuum in education. His voice has been almost "as a voice crying in the wilderness." Regular monthly postgraduate courses were begun in 1948 for serious education and training in respiratory resuscitation. One of its aims was to place resuscitation on a professional basis.

In 1950, Beck, Rand, and the author, with the sponsorship of the Cleveland Area Heart Society, inaugurated what is thought to be the first course of its kind and the first concerted attempt by the medical profession to establish a practical educational program for the prevention and treatment of cardiac arrest. Why this queer lack of knowledge prevailed in medical educational circles is difficult to explain. This subject from 1902 to 1950 seemed to be in an underground tunnel of despair, and then it suddenly emerged into the light of practicality. Some 1700 surgeons, anesthetists, dentists, and nurses have participated in this course to date. Geographically they have come from the four corners of the United States and from many foreign countries. This course, which started out almost as an orphan, seems to be satisfying a real need.

It is believed that the first malpractice suit in this field was taken to a court and jury in Cleveland, Ohio, on February 18, 1952. The plaintiff charged the surgeon and hospital with negligence for not attempting a cardiac resuscitative procedure. No judgment against the defendants was obtained; consequently a lawsuit precedent was not set. Settlements out of court do not set a precedent. It is generally felt that society is entitled to demand a reasonable attempt to resuscitate those patients who die in the operating room. Success in the application of resuscitative measures cannot be considered a requirement.

Experience leads us to believe that the time has arrived when resuscitation procedures can and must be included in the treatment of cardiac stoppage from acute coronary insufficiency. There have been several reports[8] on record since 1955 of people who have been successfully revived even after suffering apparent death from coronary occlusion. Many of these hearts will beat again if provided a second chance. Death can apparently occur from minimal myocardial damage, according to Yater and Beck.

The extramural scope of this life-saving procedure is enlarging, and new dimensions are gradually being added. Nevertheless, in resuscitation too many physicians continue to focus their attention upon the restoration of the heart beat, and as an afterthought or minor part of the procedure, upon the support of the respiratory system. This is in direct opposition to the accepted procedure.

Medical books devoted entirely to resuscitation are relatively few. The *Art of Resuscitation* (respiratory) by Paluel Flagg[9] remains a monument and shining beacon in this field. The *Manual on Cardiac Resuscitation*[10] by the author is now in its second edition and also is being published in Spanish. Doctor Sergei Kurashov, the Minister of Public Health of the Russian Federated States, recently told the author that this manual has been abstracted and sent to every single hospital in that country.

In September, 1958, the author had the rare privilege of visiting the Institute of Resuscitation in Moscow. Here fifty doctors are employed solely in basic research on resuscitation under the direction of Professor V. A. Negovsky. Each hospital in Russia has a department of resuscitation. During major operations there are stand-by resuscitation teams which take care of parenteral fluids and transfusions and other preventive measures. They are also ready to take over in such emergencies as profound shock and clinical death. Intra-arterial transfusions under these circumstances are preferred and given.

It occurred to Flagg that his course which he was giving in New York and our course in Cleveland complemented each other. Respiratory resuscitation can prevent cardiac arrest. However, should clinical death ensue, there remains the hope and reality of successful cardiac resuscitation. Thus the National Resuscitation Society has now inaugurated a didactic and clinical course in respirocardiac resuscitation which is to be given every two months at the New York Academy of Sciences under the direction of Doctors Flagg and Hosler. [This course was described by Dr. Flagg in the December, 1958, issue of this Journal—Ed.]

* By personal discussion, V. A. Negovsky is in agreement with this.

Conclusion

Resuscitative measures date back to antiquity, yet in the middle of this twentieth century, respirocardiac resuscitation is in its infancy. It will encompass ever-widening horizons before the turn of the twenty-first century. We naturally hope for this spread of interest, and we are endeavoring to improve our methods so that cardiac arrest may be successfully and effectually treated without open cardiac massage.[11] The author has found in a series of dog experiments that external defibrillation can be successfully performed with a prompt return of circulation provided that not more than an average of 50* seconds has elapsed. In similar experiments with periods of two minutes or longer, the supplementary procedure of intra-arterial perfusion of glucose and adrenalin restored the heart beat and circulation. Nevertheless, as of this moment, the greatest opportunity for success arises from first re-establishing the respiratory system, followed by open chest cardiac massage, carried out within the so-called time limit of four minutes.

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The Query Corner

READERS are invited to submit queries on all aspects of cardiovascular diseases. Insofar as possible these will be answered in this column by competent authorities. The replies will not necessarily represent the opinions of the American College of Cardiology, the JOURNAL or any medical organization or group, unless stated. Anonymous communications and queries on postcards will not be answered. Every letter must contain the writer's name and address, but these will not be published.

Letter to the Editor

Dear Sir:

I would like to call your attention to the reply in The Query Corner of the November, 1958, issue regarding Oleomargarine Prepared from Corn Oil. The reply states that this margarine is "prepared wholly from corn oil."

The approximate composition of Emdee Margarine, which was published by the Pitman-Moore Company, shows that this margarine contains 15 per cent vegetable butter. The following is a reply which I received from Dr. James T. Lowe, of the Pitman-Moore Company:

> This will reply to your inquiry of May 7 with further reference to the composition of our Emdee Margarine.
>
> The vegetable butter, as we reported, is technically hardened coconut oil, and it has a very low iodine number ranging downward from 5.0. The principal fatty acids in coconut oil are lauric—45–51%; myristic—17–18%; palmitic—8–10%; and a number of smaller chain acids such as capric and caprylic.
>
> While coconut oil alone has been shown to increase blood cholesterol levels, our own clinical findings, as well as those in the literature, indicate that when it is used with a high proportion of unsaturated fatty acids, such as contained in corn oil, there will be a definite lowering in blood cholesterol levels.

You will note that this vegetable butter is coconut oil, and since coconut oil contains only 2 per cent linoleic acid and 82 per cent saturated acid, I think this popular impression should be corrected.

Aside from the controversy as to whether or not a low-fat, low-cholesterol diet is indicated, I feel that these special preparations should state the facts to the medical profession and to the public. It seems pointless to advise a patient to use skim milk instead of whole milk and yet allow him Emdee Margarine, which contains 17 per cent coconut oil.

JACOB ALPERIN, M.D.
Memphis, Tenn.

Surgery for Coronary Disease

Query: What are the current indications and contraindications for surgery in coronary artery disease?

Answer: As a cardiovascular surgeon, this consultant knows perfectly well that at the present time surgery for coronary disease is not a curative procedure. This refers to the Beck 1, Thompson and Vineberg procedures. All we are trying to accomplish is to choose the individual who is likely to have myocardial infarction and try to prevent "mechanism death." I do not believe we can do any more than that. We therefore look for the individual who has progressively severe angina or one who has already had a myocardial infarction. We prefer that this patient have a small heart, not be very hypertensive, and not be in congestive heart failure. The electrocardiogram should reveal evidence of coronary insufficiency either at rest or after an exercise test. After this the selection of patients rests pretty much on the presence of contraindications.

Coronary surgery can now be carried out with a very small risk (in the range of 2 or 3 per cent)

provided one does not step beyond certain contraindications when selecting the patients. The most important one is congestive heart failure. When a patient with coronary disease has developed congestive failure it spells diffuse myocardial fibrosis. The operative mortality is high and the results are poor. Second, the patients with hypertension and cardiac enlargement have an increased operative risk and the results may not be uniformly good. Even in this group, however, although the effects cannot be prognosticated, a good result often can be obtained, but of course the risk is greater.

ALVIN A. BAKST, M.D.

Causes of Auricular Fibrillation

Query: What are the common underlying causes of auricular fibrillation?

Answer: There are many causes of auricular fibrillation. The etiology is different in every patient and depends upon the type of cardiac involvement present. For example, a patient with carcinoma of the lung can develop auricular fibrillation if the metastatic tumor invades and infiltrates the auricle. On the other hand, the auricular fibrillation which occurs in patients with mitral stenosis is due to distension of the left auricle. This is different from the auricular fibrillation of older patients with coronary disease or myocardial infarction where there is ischemia or even actual infarction of the auricle. Sometimes the auricular fibrillation may be congenital and often it is undoubtedly emotional in origin. For example, it can be demonstrated that soldiers suffering from combat fatigue or neurocirculatory asthenia may develop auricular fibrillation as well as other electrocardiographic changes when they are shown pictures of battle scenes. This obviously is an example of psychogenic auricular fibrillation.

MYRON PRINZMETAL, M.D.

Transaminase in Pericarditis

Query: Are serial transaminase tests of more value in distinguishing pericarditis from infarction than the electrocardiogram? Do you feel that at times the transaminase test is delayed in mild cases of infarction?

Answer: Serial transaminase tests are of greater value than the electrocardiogram in distinguishing pericarditis from myocardial infarction only in those instances where the electrocardiogram fails to show abnormal Q waves. Even then it must be realized that experience with these tests is still limited and that none of the laboratory tests can do much more than supplement the complete clinical evaluation; they cannot replace it. The concomitant use of the fibrinogen polymerization test enhances considerably the usefulness of the serum enzyme tests.

We have never come across the finding of a delayed positive transaminase test in myocardial infarction. Both clinical and experimental experience has demonstrated the semiquantitative relationship of the abnormal serum enzyme (SGO-transaminase and aldolase) levels to the extent of myocardial infarction. No time relationship of the type referred to in the query has been noted.

RUDOLPH E. FREMONT, M.D.

Book Reviews

Fundamentals of Electrocardiography and Vectorcardiography, by Lawrence E. Lamb. Charles C Thomas, Springfield, Ill., 1957, pp. 142, $9.50.

The opening chapter, "Fundamental Vector Concepts," is elegantly lucid and one of the best the reviewer has read. Information regarding cellular polarization and depolarization has been discussed in greater detail in other textbooks, but they are shrewdly directed to the understanding of vectorcardiography. In the presentation of vectorcardiography, the author employs a semiquantitative electrode placement which requires lead measurements from the chest x-ray. Despite the obvious clinical drawback of x-ray measurements, this represents a meritorious attempt at vectorcardiographic lead standardization. However, the author would have to demonstrate by more illustrations that his lead placement enjoys clinical advantages considerably superior to the Grishman modification of the Duchosal-Sulzwe cube system or any other system. Indeed, the problem of lead systems bedevils clinical vectorcardiography today. Only a few directly recorded vectorcardiographic loops are shown and the remainder of the subject is illustrated by wire loop models. Many readers might prefer the former rather than the latter.

The concept of right ventricular dilatation is emphasized at the expense of right ventricular hypertrophy, and the distinction between the two requires more cogent discussion. The vector loop models of right and left ventricular hypertrophy and bundle branch block clearly show the initial and terminal 0.04 second vectors. Only two loop models of myocardial infarction are published. One wonders why so much space is devoted to accelerated conduction in this relatively small text and why the appearance of tall U waves in hypopotassemia is not mentioned, although they appear to be visible in Figure 138. In a number of electrocardiograms, the technician's original lead numbering appears and it is hoped that in subsequent editions this will be erased. Likewise, it is hoped that some of the illustrations will appear closer to the text discussion. The illustrations have been thoughtfully selected.

The author has some refreshing ideas regarding the inadequacy of the intrinsicoid deflection in the diagnosis of left ventricular hypertrophy and about the effects of respiration on the electrocardiogram. He contends with some proof that respiratory QRS changes are not due entirely to axis shifts, as conventionally believed, but are related to alterations in ventricular stroke volume. This is a stimulating concept which will require further investigation with other tools. The sketches depicting the progress of septal and ventricular excitation in different cardiac disorders are first-rate and are neatly applied to the understanding of the vectorcardiogram. However, they do not require a full page, and summarizing them compactly would make a valuable pedagogic contribution. The author's chart for calculating the spatial QRS-T angle will be appreciated by vectorcardiographers.

The author evidently has a clear grasp of his subject and has been well trained in basic concepts drawn from the physical laws of bioelectric currents. The interested reader will find concepts trenchantly presented, as for example the difference between polygon and coordinate graphs.

Dr. Lamb's book is one of the few American texts to discuss the European ideas of electrical moment as applied clinically, and this is both courageous and laudable. The reviewer also applauds Dr. Lamb's acknowledgment to Pierre Duchosal, whose singular contributions to vectorcardiography have not received the accolade they deserve. STEPHEN R. ELEK, M.D.

Plastic Arterial Grafts by W. Sterling Edwards, Thomas, Springfield, Ill., 1957, pp. 126, $4.50.

The monograph entitled *Plastic Arterial Grafts*, written by one of the pioneers and present authorities in this field, is in actuality more comprehensive than the title implies. The prelim-

inary sections of the monograph concern an excellent account of the historical development of arterial-replacement graft materials. This aspect of the work culminates in an objective assessment of their present status, with no display of partisanship for the author's personal contributions to the field. The body of the publication is given over to an excellent presentation of the clinical management of injuries and disease of small and large arteries in different locations. This serves as a frame of reference for acquainting the reader with the practical aspects of blood vessel replacement.

The monograph is a valuable contribution from several standpoints. First of all, in any rapidly developing field a periodic inventory of our knowledge is essential so that confusion is minimized. The author has fulfilled this mission by a scholarly, well-documented definition of the present status of plastic arterial grafts. Secondly, although it offers little new to the cardiovascular surgeon, the surgeon doing occasional vascular surgery, the student, and the investigator will find the monograph an extremely valuable reference source. Finally, as indicated by the last section, entitled "Unsolved Problems in the Field of Plastic Arterial Grafts," the investigator will find guideposts to future progress in this field. The monograph is attractive, and very legible, and the illustrations are well chosen and clearly reproduced.

RALPH D. ALLEY, M.D.

L'Activité Électrique Auriculaire: Normale et Pathologique, by Paul Puech. Masson & Cie, Paris, 1956, pp. 286, 2,600 fr.

Monographic presentations of limited subjects can form an important aid to workers and investigators in the field if subject matter, review of literature, and bibliography are dealt with in an essentially complete fashion. Puech achieves this goal admirably in his book on the electrical activity of the atria in normal and pathologic states. In 281 pages of text with 85 excellent illustrations and with 575 cited references, a complete account of the electrical behavior of the atria is given. The information accumulated can be regarded as complete, with all phases of the problem discussed critically and lucidly. The book is of such authoritative quality that it should be part of the library of every cardiologist and investigator of electrocardiography and electrophysiology. The text is well printed, and the reproduction of illustrations is satisfactory.

ARTHUR GRISHMAN, M.D.

Peripheral Circulation in Health and Disease, by Walter Redisch, Francisco F. Tangco, and R. L. deC. Saunders. Grune & Stratton, Inc., New York, 1957, pp. 154, $7.75.

This book consists of succinct, thumb-nail sketches of the physiology, pathology, and clinical status of almost every peripheral vascular disease and some systemic states. These are presented in almost outline form, much as a medical student might make up before an examination. Treatment is similarly presented. However, there is a comprehensive list of references to which those interested can go for more detailed and comprehensive information. This book is almost devoid of personal opinion. When one is given it is not accompanied by a detailed presentation. There is for example, on page 91, the statement that certain treatments "have been advocated. In our hands results have not been encouraging." A bald statement, which, if false, will mislead a student. For the experienced reader it does not provide information needed for its evaluation. The relationship of cigarettes to thromboangiitis is not stressed. The active superficial phlebitis of this disease always subsides in three weeks after the last cigarette unless ulceration is present. The use of alcohol in arterial insufficiency is overstressed, since little can bypass the arterial block while more can go to the brain where it makes the patient "accident prone."

The final chapter of this book presents an interesting anatomic study of the arterial circulation of muscles. This demonstrates that its character depends on the type of muscular attachment. The muscles are supplied by direct arterial branches and by arteries from adjacent structures. These, after supplying the muscles, penetrate the fascia to supply the skin. This study negates the theory of separate blood supplies for skin and muscles which the preceding clinical chapters of this book keep stressing. This also supports the claim that when a vasodilator causes erythema it probably also reflects the extent and degree of vasodilatation in the muscles. This is not true for a rise in skin tem-

perature, which can represent many other physical changes.

The book should be in hospital libraries, where its brevity would be an asset. Though references may become outdated rapidly in an active field of inquiry, they are numerous and relevant and therefore will remain useful to those interested in peripheral vascular disease.

ISIDOR MUFSON, M.D.

Chemistry of Lipides as Related to Atherosclerosis—A Symposium, compiled and edited by Irvine H. Page. Charles C Thomas, Springfield, Ill., 1958, pp. 342, $8.50.

The symposium consists of 17 stimulating papers presented on May 7 and 8, 1957, under the auspices of the National Heart Institute, United States Public Health Service.

In the introduction Page discusses, among other aspects of the problem, the "phenomenal increase of interest in the subject of atherosclerosis" in the past ten years, the major importance of lipids in the problem of heart disease, and the role of factors "other than fat" in atherogenesis.

A. T. James presents an informative paper on the behavior of unsaturated fatty acids in gas-liquid chromatography. In patients with coronary artery disease a higher oleic acid content was found in the plasma neutral fat than in the controls. The essential fatty acids were not found to be a factor in this disease.

The bulk of the book is devoted to three major topics. Lipid chemistry and distribution is extensively discussed in articles by F. M. Mattson (fatty acids), B. F. Daubert and I. I. Rusoff (triglycerides), D. J. Hanahan (phospholipids), H. E. Carter (sphingolipids), P. P. Cohen (tissue lipoproteins), and J. L. Oncley (plasma lipoproteins). The second group of papers is concerned with an exhaustive presentation of absorption and transport of lipids. The authors are B. Borgström (digestion and absorption of fat), D. B. Zilversmit (the turnover of plasma lipids), E. D. Korn (lipoprotein lipase), V. P. Dole (transport of nonesterified fatty acids in plasma), D. S. Fredrickson *et al.* (the early steps in transport and metabolism), and E. H. Ahrens *et al.* (dietary fats and human serum lipid levels). The third and final group of papers deals with the cellular metabolism of lipids. The authors are A. L. Lehninger (oxidation of fatty acids), R. G. Langden (biosynthesis of fatty acids in cell-free liver preparations), S. Gurin (biosynthesis of cholesterol), and E. P. Kennedy (enzymatic synthesis of phospholipids and triglycerides).

The contributions are written by the most qualified experts in their respective fields. They are of high quality and represent an excellent review of important research. Although highly specific, the papers are well written and easily understandable to the physician and experimental worker interested in heart disease, with emphasis on clinical and biochemical aspects of atherosclerosis. A lively and very instructive discussion follows almost all of the articles. The one following the paper of Ahrens *et al.* on dietary fats occupies 14 pages and is of particular interest. As an important and complete source of information up to May, 1957, the book can be highly recommended.

DAVID ADLERSBERG, M.D.

RECEIVED FOR REVIEW

All books received will be acknowledged in this column. Insofar as possible, as space permits, books of special interest will receive more extensive reviews.

Differentialdiagnose innerer Krankheiten by Robert Hegglin. Georg Thieme Verlag, Stuttgart, 1958, pp. 819, DM 79.50 ($18.85).

Radioisotope in der Herzdiagnostik by Hans Ludes and Gerhard Lehnert. Fischer Verlag, Jena, pp. 107, DM 16.90.

Atlas intracardialer Druckkurven by Otto Bayer and Hans Helmut Wolter. Georg Thieme Verlag, Stuttgart, 1959, pp. 185, DM 68.

Der Menschliche Herzaschlag, by Franz A. N. Kienle. Verlag Wolfgang Weidlich, Frankfurt, 1958, pp. 114, DM 39.80.

Vascular Surgery by Geza de Takats. Saunders, Philadelphia, 1959, pp. 726 with 382 illust., $17.50.

Long-Term Illness: Management of the Chronically Ill. Patient, edited by Michael G. Wohl. Saunders, Philadelphia, 1959, pp. 748, $17.00.

Don't Worry About Your Heart by Edward Weiss. Random House, New York, 1959, pp. 203, $3.95.

College News

AMERICAN COLLEGE OF CARDIOLOGY

Preliminary Program, Eighth Annual Meeting

Dr. John S. La Due, Chairman of the Scientific Program Committee, has announced the following preliminary program to be presented at the Eighth Annual Meeting of the College, to be held at the Benjamin Franklin Hotel, Philadelphia, Pennsylvania, May 26 to 29, 1959.

Scientific Sessions

TUESDAY, MAY 26

9:00–10:30 A.M.	Papers presented by Philadelphia group, arranged by ROBERT P. GLOVER.
11:00 A.M.–5:00 P.M.	*Symposium on Biophysiology of Arteriosclerosis:* Pathogenesis Biochemical Aspects Coagulation and Fibrinolysis Genetics and Epidemiology Hormonal Factors Diet and Other Aspects of Treatment

WEDNESDAY, MAY 27

9:00 A.M.–12 NOON	Papers presented by College members.
2:00–3:30 P.M.	*Symposium on Aviation Medicine.* Moderator: ASHTON GRAYBIEL, Pensacola, Fla.

THURSDAY, MAY 28

9:00 A.M.–12 NOON	*Symposium on Use and Abuse of the Pump Oxygenator.*
2:00–3:00 P.M.	Annual Guest Lecture: *Role of Fibrinolysis in Heart and Peripheral Vascular Disease.* TAGE OSTREP, Copenhagen.
3:30–5:30 P.M.	*Symposium on Complications of Cardiac Surgery.* Moderator: OSLER ABBOTT, Atlanta, Ga.

FRIDAY, MAY 29

9:00–11:00 A.M.	*Symposium on Auscultation.* Moderator: W. PROCTOR HARVEY, Washington, D. C.
11:30 A.M.–12:30 P.M.	*Symposium on Intracardiac Phonocardiography and Chest Wall Vibrations.* Moderator: ALDO A. LUISADA, Chicago, Ill.
2:00–3:30 P.M.	*The Present and Future of Cineangiocardiography.*

Fireside Conferences

The following topics will be discussed:

- Ballistocardiography
- Heart Disease and Pulmonary Function
- Electrolytes in Congestive Failure
- Subendocardial Infarction
- Myocardial Metabolism
- Fibrinolysis in Heart Disease
- Surgery of Aortic Valve Disease
- WPW Syndrome
- Chlorothiazide and Analogues
- Surgery of Coronary Heart Disease

The program will also include the Annual Groedel Memorial Lecture and scientific exhibits on various aspects of cardiovascular disease.

All members of the College and their guests are urged to attend this interesting meeting. Early reservations should be made by writing to the Benjamin Franklin Hotel, Philadelphia, and mentioning the American College of Cardiology. Further details concerning the scientific program and other convention events will be published in the Journal.

Affiliation with A.A.A.S.

The College is now officially affiliated with the American Association for the Advancement of Science. On the roster of groups affiliated with this general association of scientists are more than three hundred of the nation's leading scientific, academic, and philosophical societies. The Association crosses all of the various disciplines and provides a central focus and exchange point. All members of the College will shortly receive an invitation to join the Association directly and receive the Association's periodical, *Science*. Dr. George W. Calver of Washington, D. C., has been appointed to represent the College in the Council of the Association.

HERBERT EICHERT

HERBERT EICHERT of Miami, Florida, Fellow of the College since 1953, was killed in an automobile accident on February 3, 1959. Dr. Eichert was graduated from the University of Maryland, receiving a Bachelor of Science in Pharmacy in 1928 and a Doctor of Medicine degree in 1932. He was qualified under the American Board of Internal Medicine in 1941 and received his subspecialty certification in Cardiology in 1946. In 1950 he served as President of the Miami Heart Association and he was a member of the Scientific Council of the American Heart Association.

Dr. Eichert served the College well, and much of the growth of the College in the State of Florida may be traced to his efforts. He served on the Board of Trustees, as Vice President of the College in the administration of Dr. Simon Dack, and was re-elected to the same post in the administration of Dr. George Meneely. Committee assignments were taken very seriously by Dr. Eichert and he was frequently called upon by the Central Office to help in validating the status of candidates for Fellowship. For this purpose he made full use of his wide contacts in the United States, Mexico and South America, and his credentials reports were unusually complete and perceptive. For this reason he was twice appointed to special review committees on candidates' credentials. We who sat with him at these sessions remember that they lasted well into the morning, and to the very end Herb gave each candidate his complete and unhurried attention and judgment.

At the time of his death, Dr. Eichert was 51 years old. We shall miss his energy, enthusiasm, and fellowship. PHILIP REICHERT

Coming in the April issue . . .

ECG Exercise Tolerance Tests . . . ECG in Auricular Overloading . . .
Intracardiac Electrocardiography . . . Review of Tricuspid Disease . . .